SYNTHESIS, CHEMICAL AND SPECTRAL STUDIES OF MODIFIED STEROIDS

RESUME

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

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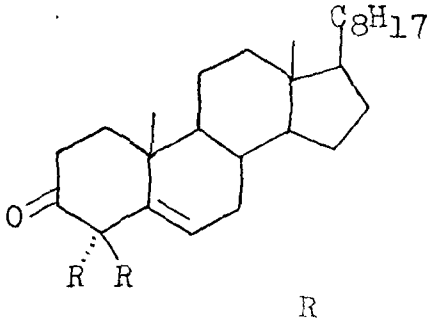
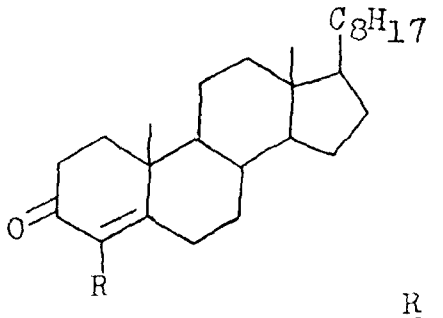
PART ONE

Steroidal Tetrazoles

The physiological properties of the steroidal alkaloids and the discovery of a variety of oxygen and nitrogen containing heterocyclic compounds with useful therapeutic values stimulated extensive research in oxygen and nitrogen containing steroids and this resulted in the preparation of a variety of oxa and aza steroids. The syntheses of steroidal tetrazoles also have become of interest in recent years because of the discovery of biological activity associated with them. Some tetrazoles are used as potential lipolysis inhibitors. A number of steroidal tetrazoles such as (V-IX) which were obtained from ketones (I-IV) were reported from our laboratory.[a]

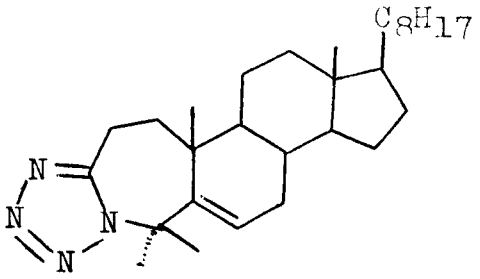


	R
(I)	CH_3
(II)	C_2H_5

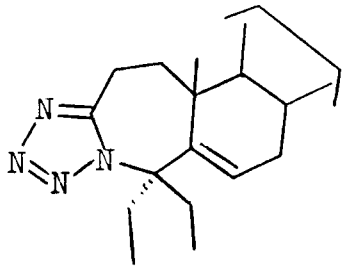


	R
(III)	CH_3
(IV)	C_2H_5

a. Shafiullah and M.A. Ghaffari, Acta, Chim. Acad. Sci(Hung.) 103, 333(1980).



(V)



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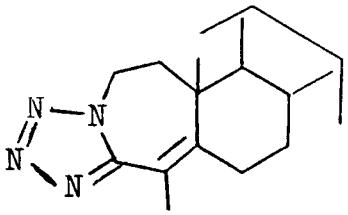

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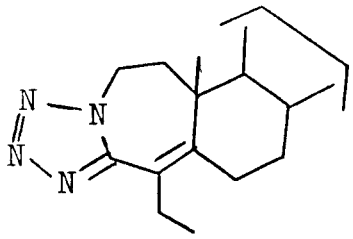
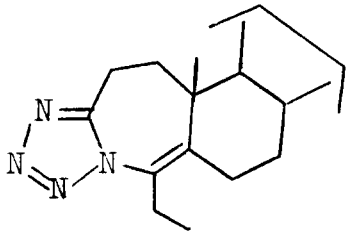
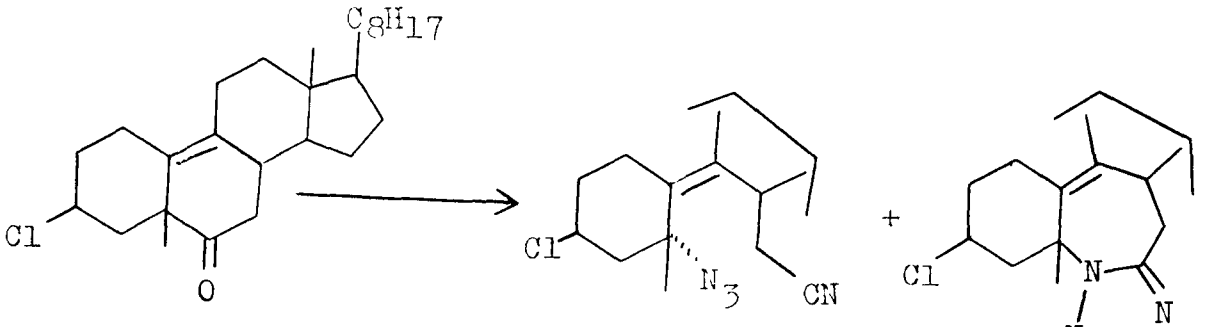


(VIII)

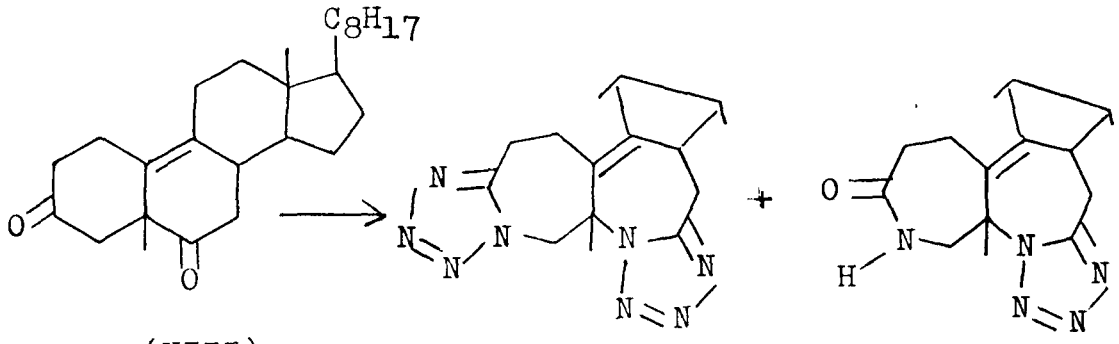


(IX)

The present work is an extension towards the syntheses of steroidal tetrazoles from the less familiar steroidal ketones, 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (X) and 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XIII). The chloroketone (X) when treated with excess of HN_3 (BF_3-etherate as the catalyst) afforded 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (XI) and 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (XII)[b]. The diketone (XIII) under similar reaction conditions furnished 4,6-diaza-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[4,3-d][6,7-d]bistetrazole (XIV) and 4,6-diaza-3-oxo-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (XV). The structures of these compounds were established on the spectral and chemical evidences.



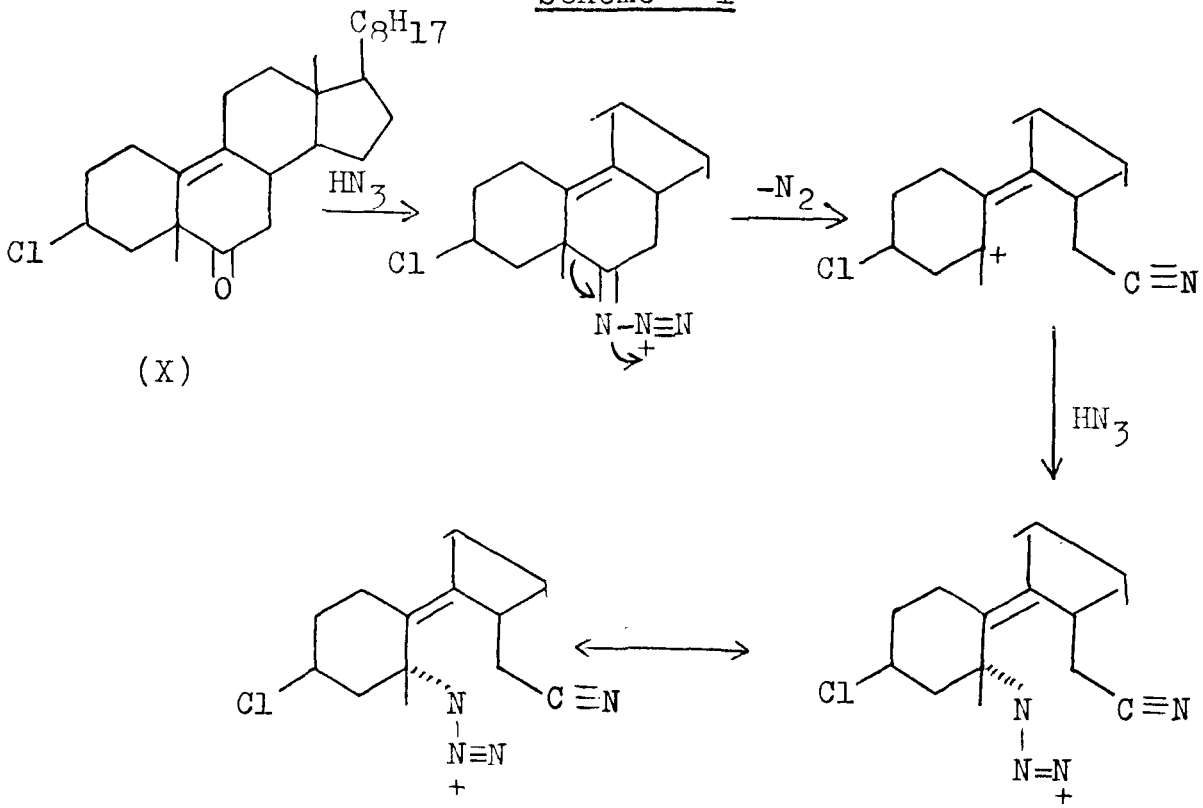
(X) (XI) (XII)



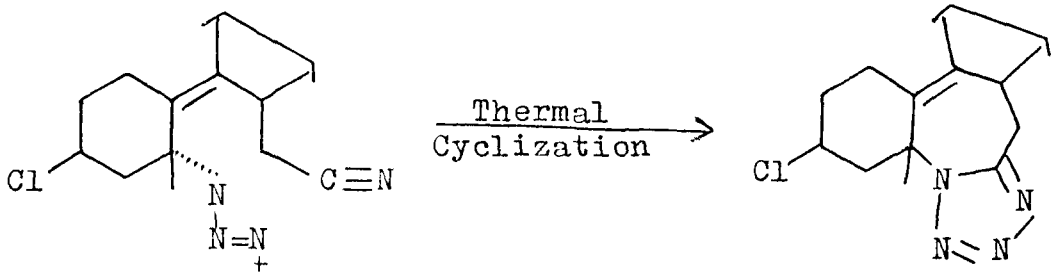
(XIII) (XIV) (XV)

The formation of nitrile (XI), tetrazoles (XII and XIV), and lactamtetrazole (XV) is proposed as follows (Scheme-1 and Scheme-2).

Scheme - 1

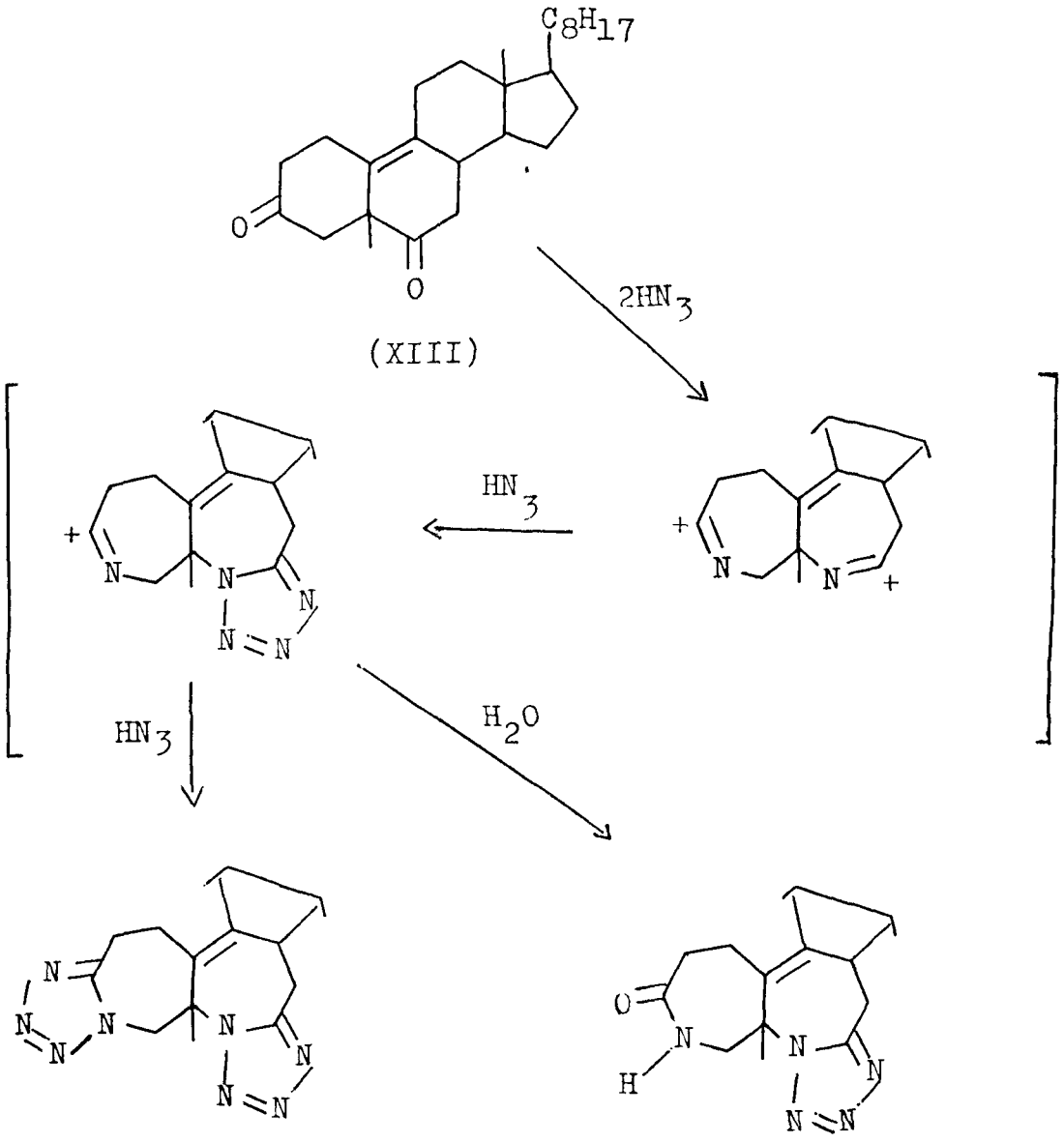


(XI)



(XI) (XII)

Scheme - 2



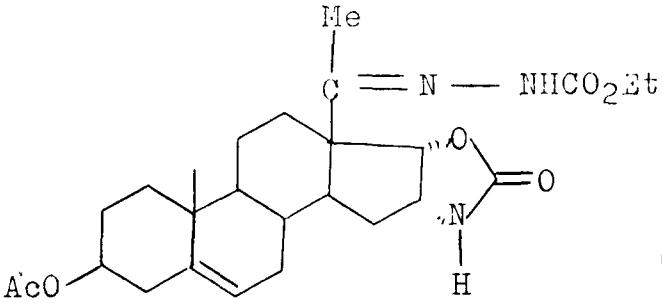
(XIII)

(XIV) (XV)

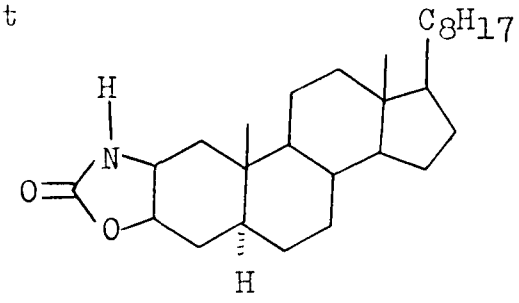
PART TWO

Steroidal Oxazolidinones

Oxazolidinones have been shown to possess various biological activities such as antibacterial, fungicidal, antiinflammatory, herbicidal, analgesic etc. A number of papers appeared describing the various methods for the syntheses of non-steroidal oxazolidinones. The literature survey revealed that no significant work has been done in the field of steroidal oxazolidinones and only a few oxazolidinones such as (XVI)[b] and (XVII)[c] have been reported.



(XVI)



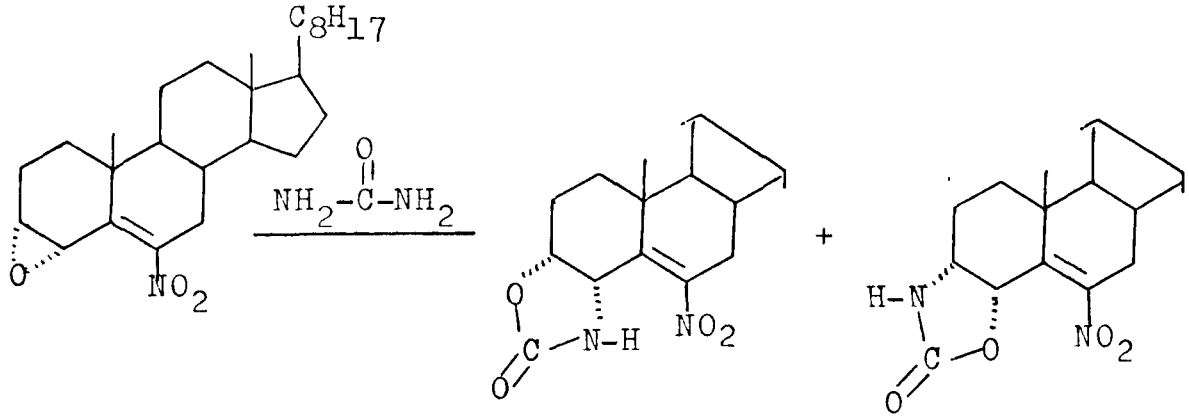
(XVII)

b. Z.I. Istomina and A.M. Turuta, Chem. Abstr., 92, 147038 (1980).

c. A.J. Jones, P.F. Alewood, M. Benn and J. Wong, Tetrahedron Lett. 1655 (1976).

This prompted us to synthesise steroidal oxazolidinones from a recently reported[d] epoxide, 3α,4α-epoxy-6-nitrocholest-5-ene (XVIII) by the reaction of urea and also of acetamide.

The epoxide (XVIII) in N,N-dimethyl formamide when refluxed with urea gave after column chromatography over silica gel 6-nitrocholest-5-eno[4α,3α-d]oxazolidin-2'-one (XIX) and 6-nitrocholest-5-eno[3α,4α-d]oxazolidin-2'-one (XX). Under identical reaction conditions the epoxide (XVIII) with acetamide provided 6-nitrocholesta-3,5-diene (XXI), 3α,4β-dihydroxy-6-nitrocholest-5-ene (XXII) and oxazolidinone (XX). Stereochemical study for the characterization of epimeric oxazolidinones (XIX) and (XX) was done with the help of NMR spectroscopy. A mechanism was also suggested for their formation.



(XVIII) (XIX) (XX)

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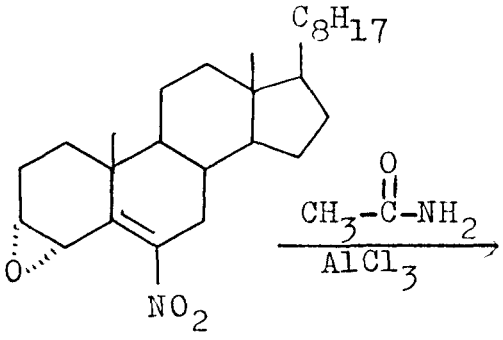
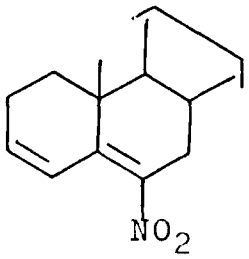
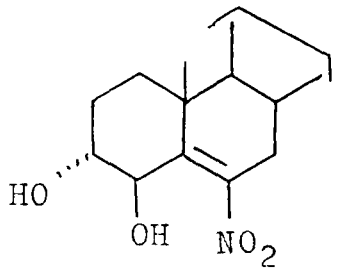
d. Shafiullah, Shakir Husain and M. Rafiuddin Ansari, Ind. J. Chem., 24B, 662 (1985).





(XVIII) (XXI)



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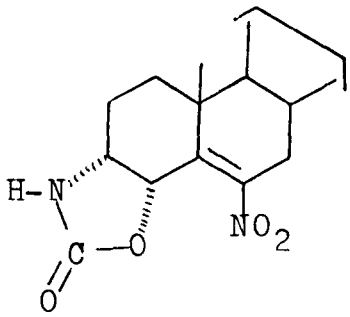
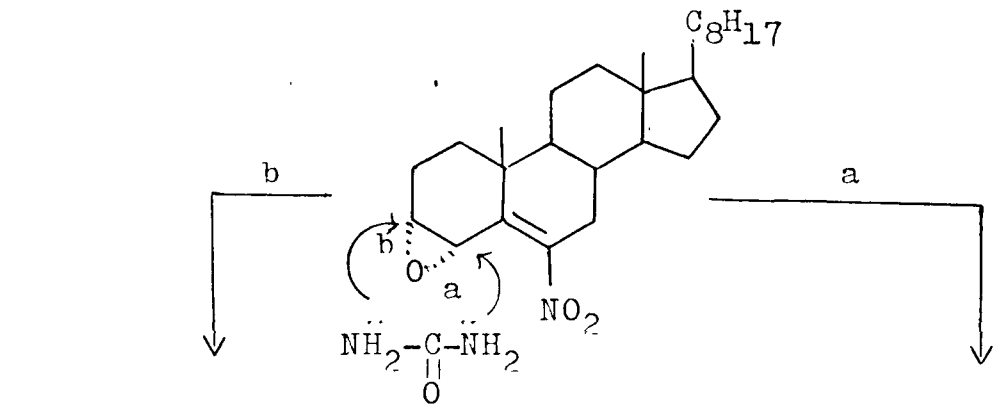


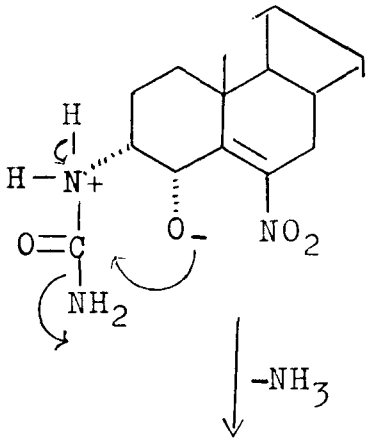
(XXII) (XX)

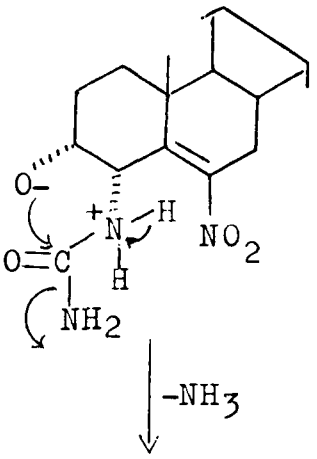
Formation of the isomeric oxazolidinones (XIX) and (XX) from the epoxide (XVIII) by the reaction of urea may be explained by the following tentative mechanism (Scheme-3).

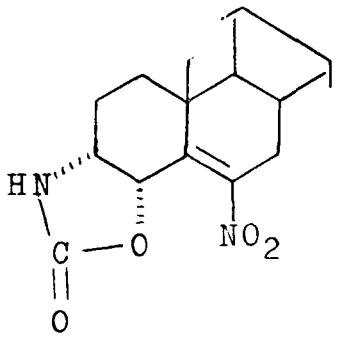
Scheme - 3

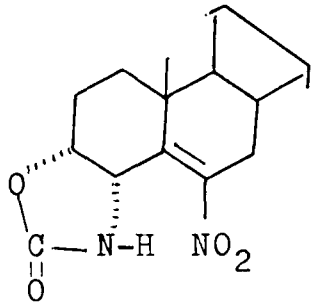


(XVIII)









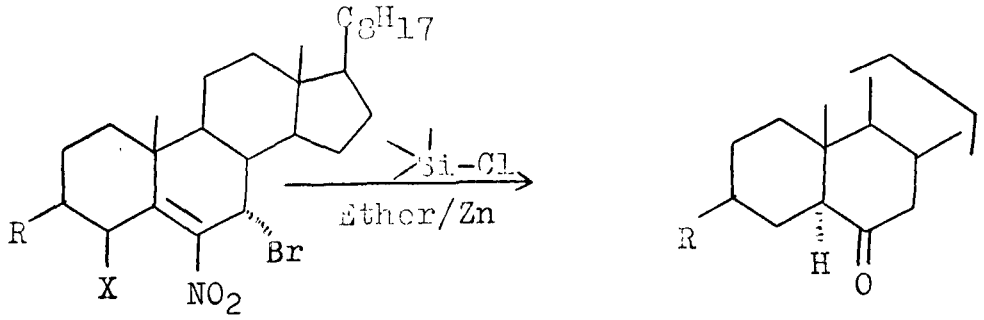
(XX)

(XIX)

PART THREE

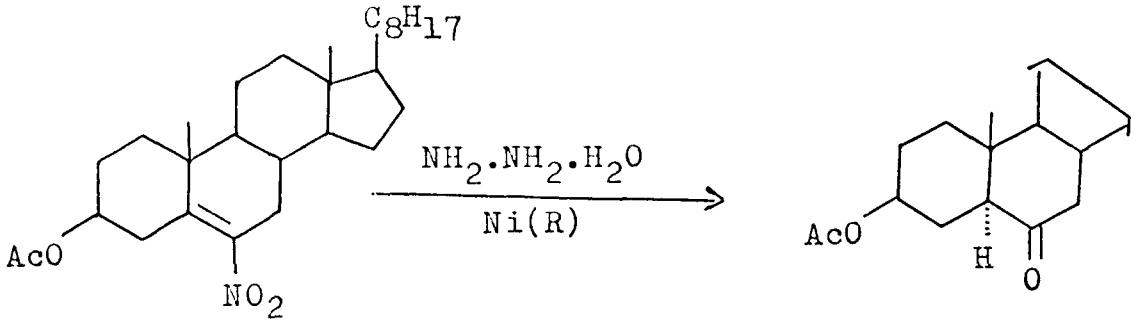
Reduction of Steroidal Nitroolefins

Reduction is one among the various reactions used in the synthetic pathway in Organic Chemistry. Many types of reagents were successfully employed for this purpose. Recently in our laboratory chlorotrimethylsilane was used to reduce the steroidal nitroolefins (XXIII, XXIV and XXV) to the corresponding ketones (XXVI, XXVII and XXVIII)[e] at room temperature, to make use of the utility of the reagent.. In present work, reduction with hydrazine-hydrate, catalysed by Raney nickel was carried out to impress upon the utility, in the syntheses of steroidal compounds. 3β-Acetoxy-6-nitrocholest-5-ene (XXIX) provided 3β-acetoxy-5α-cholestan-6-one (XXVI), 3β-acetoxy-5α-cholestan-6-one oxime (XXX) and 3β-hydroxy-5α-cholestan-6-one (XXXI) under the reduction conditions.

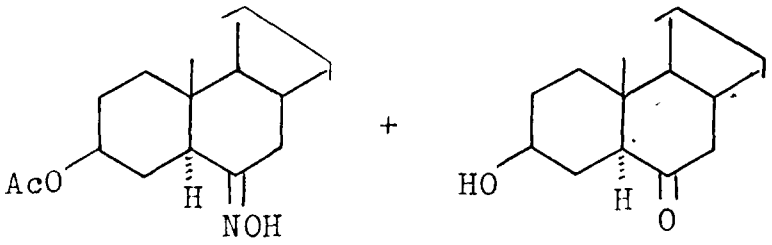


	R	X		R
(XXIII)	OAc	H	(XXVI)	OAc
(XXIV)	Cl	H	(XXVII)	Cl
(XXV)	H	Br	(XXVIII)	H

e. Shafiullah and Shakir Husain, J. Ind. Chem. Soc., 62, 163 (1985).

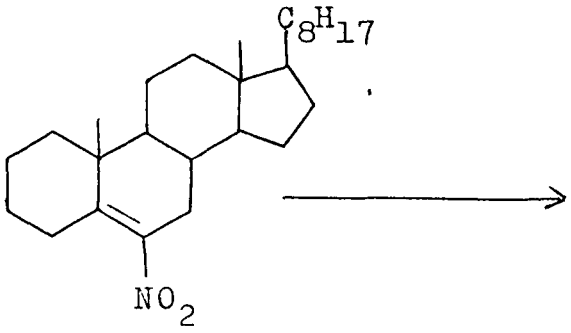


(XXIX) (XXVI)

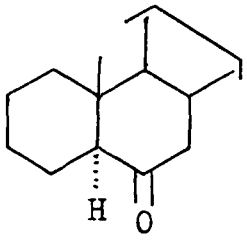


(XXX) (XXXI)

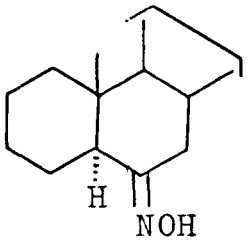
When 6-nitrocholest-5-ene (XXXII) was reduced gave the usual products, ketone and oxime (XXVIII and XXXIII) along with 6β-amino-5α-cholestane (XXXIV). Reduction of 3β-chloro-6-nitrocholest-5-ene (XXXV) gave 3β-chloro-5α-cholest-6-one (XXVII)the usual product, along with two dimers,3β,3'β-dichloro-5α,5'α-6,6'-bisazocholestane (XXXVI) and 3α,5α-3'α-5'α-cyclo-6,6'-bisazocholestane (XXXVII).



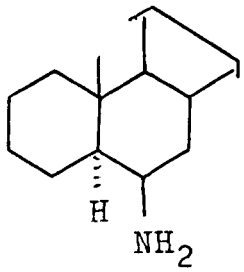
(XXXII)



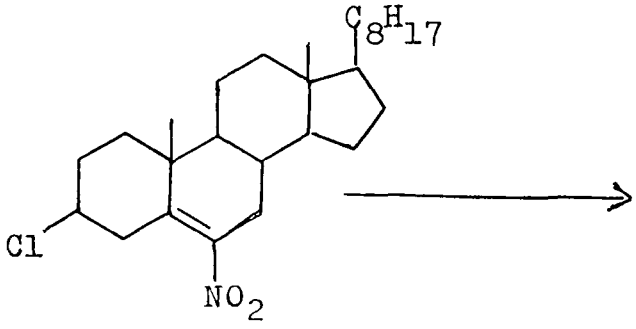
(XXVIII)



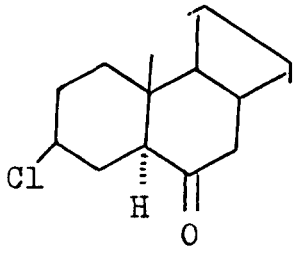
(XXXIII)



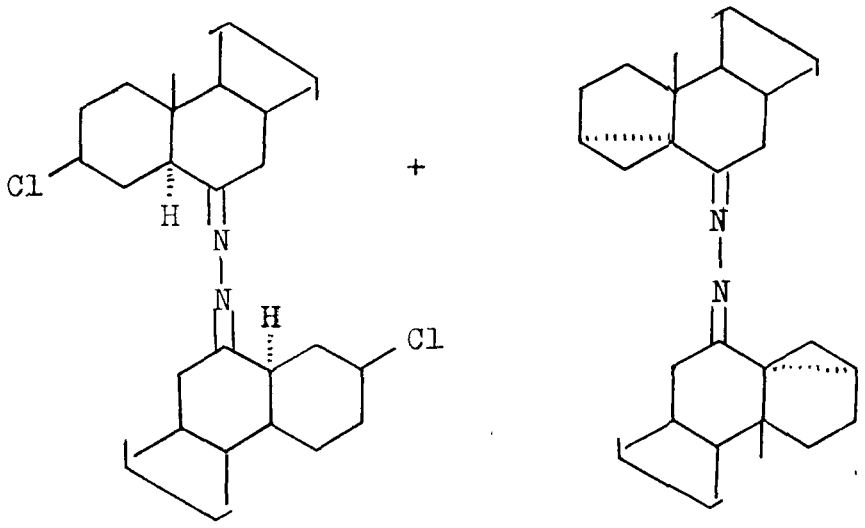
(XXXIV)



(XXXV)

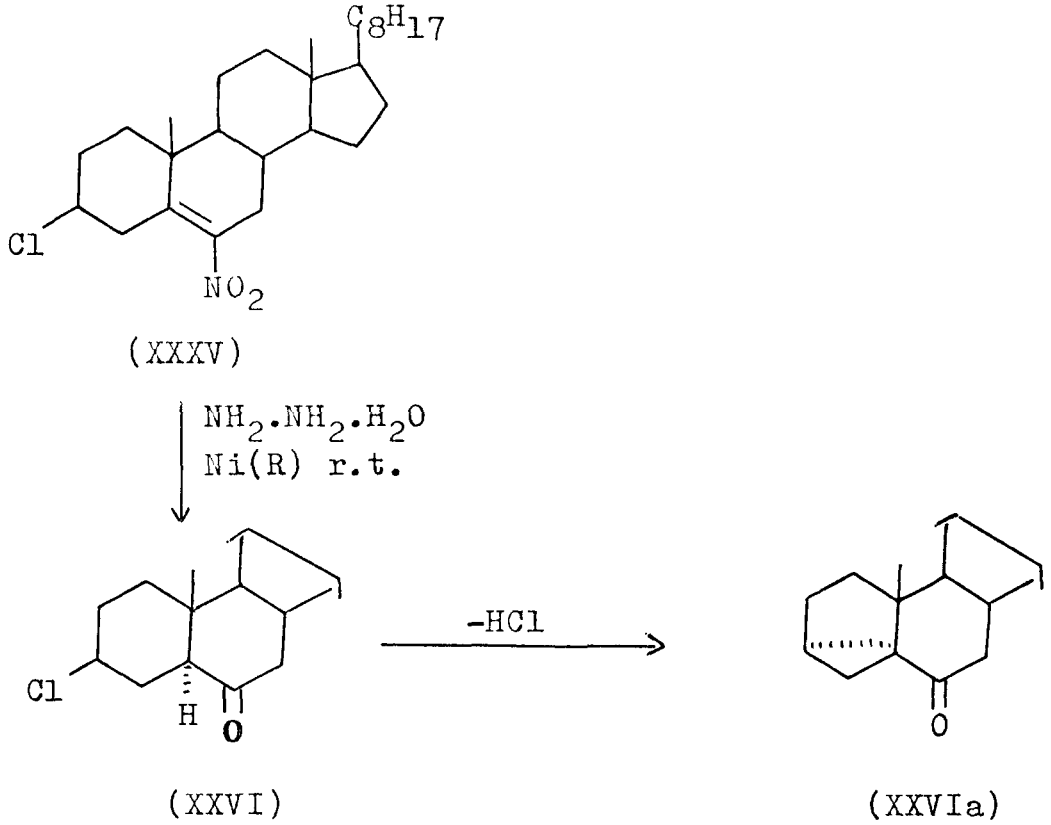


(XXVII)



(XXXVI) (XXXVII)

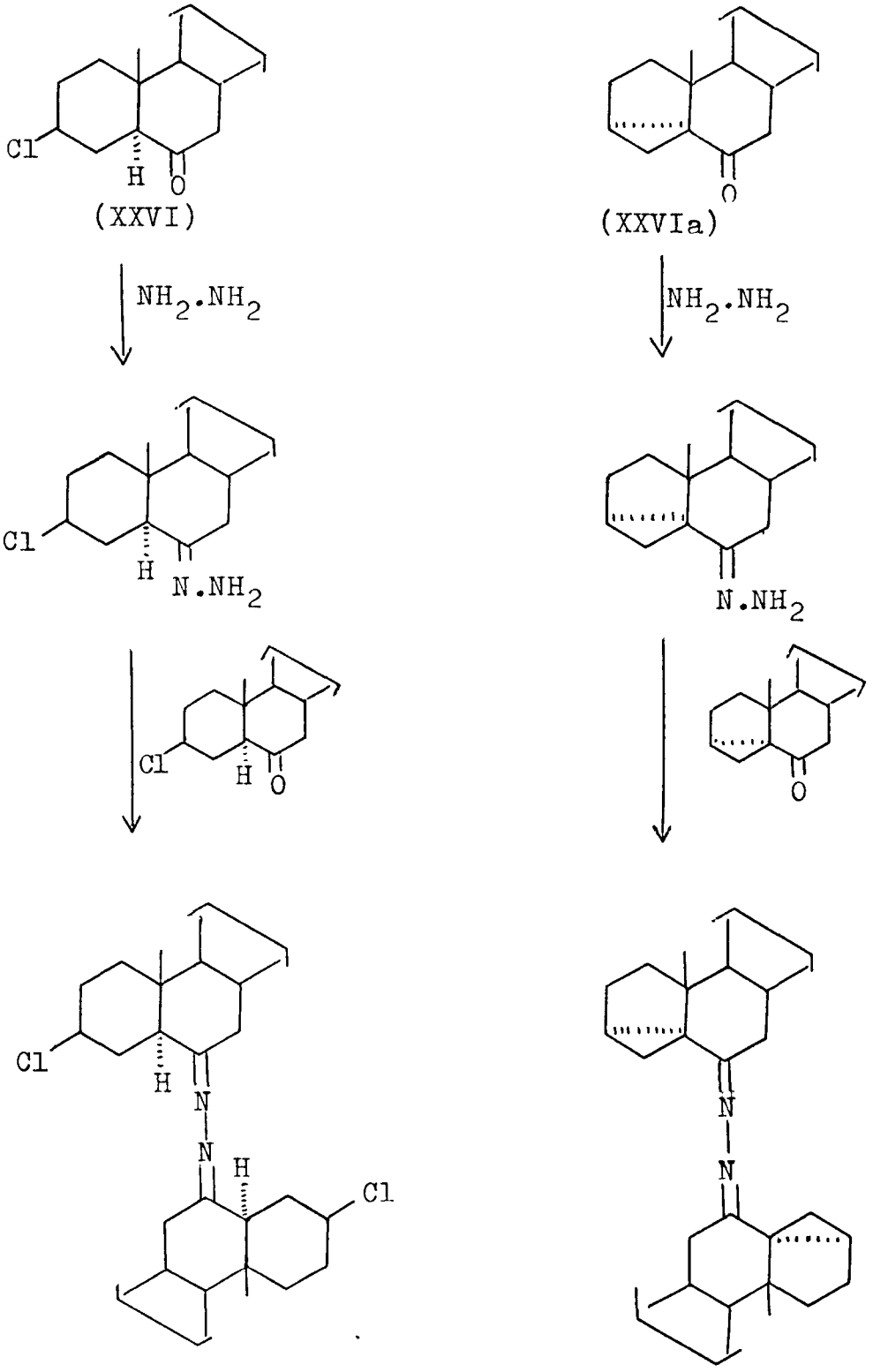
A tentative mechanism is proposed to explain the formation of the dimers (XXXVI and XXXVII) in which the ketones (XXVI and XXVIa) formed, react with hydrazine to furnish the corresponding dimers (Scheme - 4).



(XXXV)

(XXVI) (XXVIa)

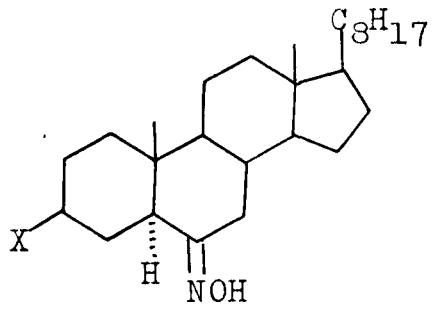
Scheme - 4


Cl
H
O
(XXVI)
$NH_2.NH_2$
Cl
H
N.NH_2
Cl
H
O
Cl
H
N
N
H
Cl
(XXXVI)
O
(XXVIa)
$NH_2.NH_2$
N.NH_2
O
N
N
(XXXVII)

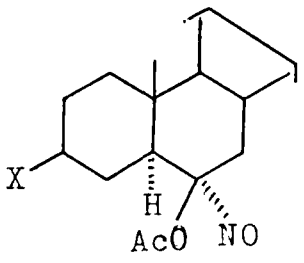
PART FOUR

Oxidation of Steroidal-6-nitroolefins with Lead Tetraacetate

Lead tetraacetate in glacial acetic acid reacts with simple alkenes, ketones, oximes, alcohols and lactones and provides a variety of products. Previous work[f,g] from our laboratory described the reaction of lead tetraacetate on steroidal oximes (XXXVIII) and interesting products such as steroidal nitrosoacetates (XXXIX) and nitroacetate (XL) were reported. In continuation to it we carried out the lead tetraacetate oxidation of steroidal nitroolefins about which no mention has been made in the literature.



(XXXVIII)



(XXXIX)

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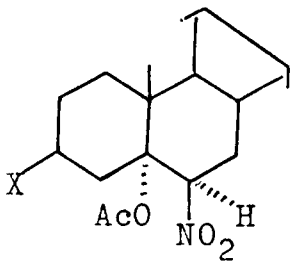

(XL)

X = H, OH, OAc, Cl, Br, I.

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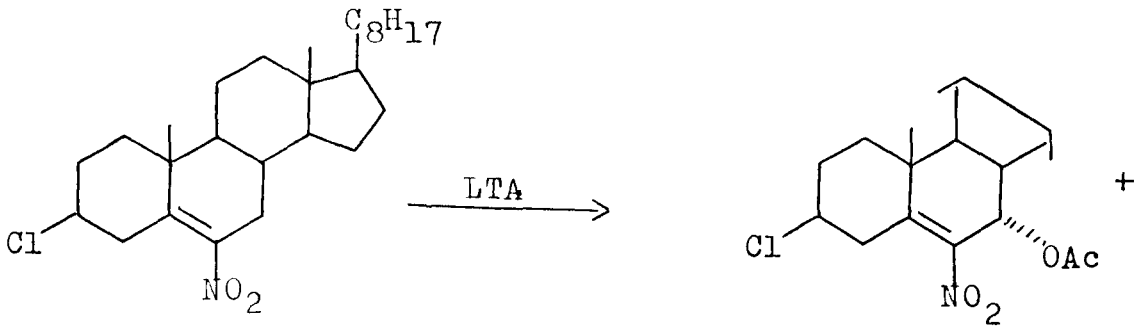
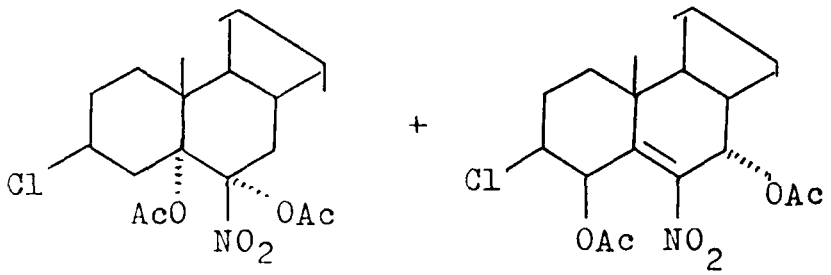
f. Shafiullah and Hasrat Ali, Synthesis, 124 (1979).

g. Shafiullah, Hasrat Ali and Shamsuzzaman, Acta. Chim. Acad. Sci. (Hung.) 107, 97 (1981).

The reaction of 3β-chloro-6-nitrocholest-5-ene (XXXV) provided the α-acetylated products (XLI and XLII) and also an addition product (XLIII)[h] where as the reaction of 3β-acetoxy-6-nitrocholest-5-ene (XXIX) and 6-nitrocholest-5-ene (XXXII) provided the conjugated nitroolefins (XLIV and XLVI) respectively. The products are characterized on the basis of their spectral and chemical studies.



(XXXV) (XLI)



(XLII) (XLII)

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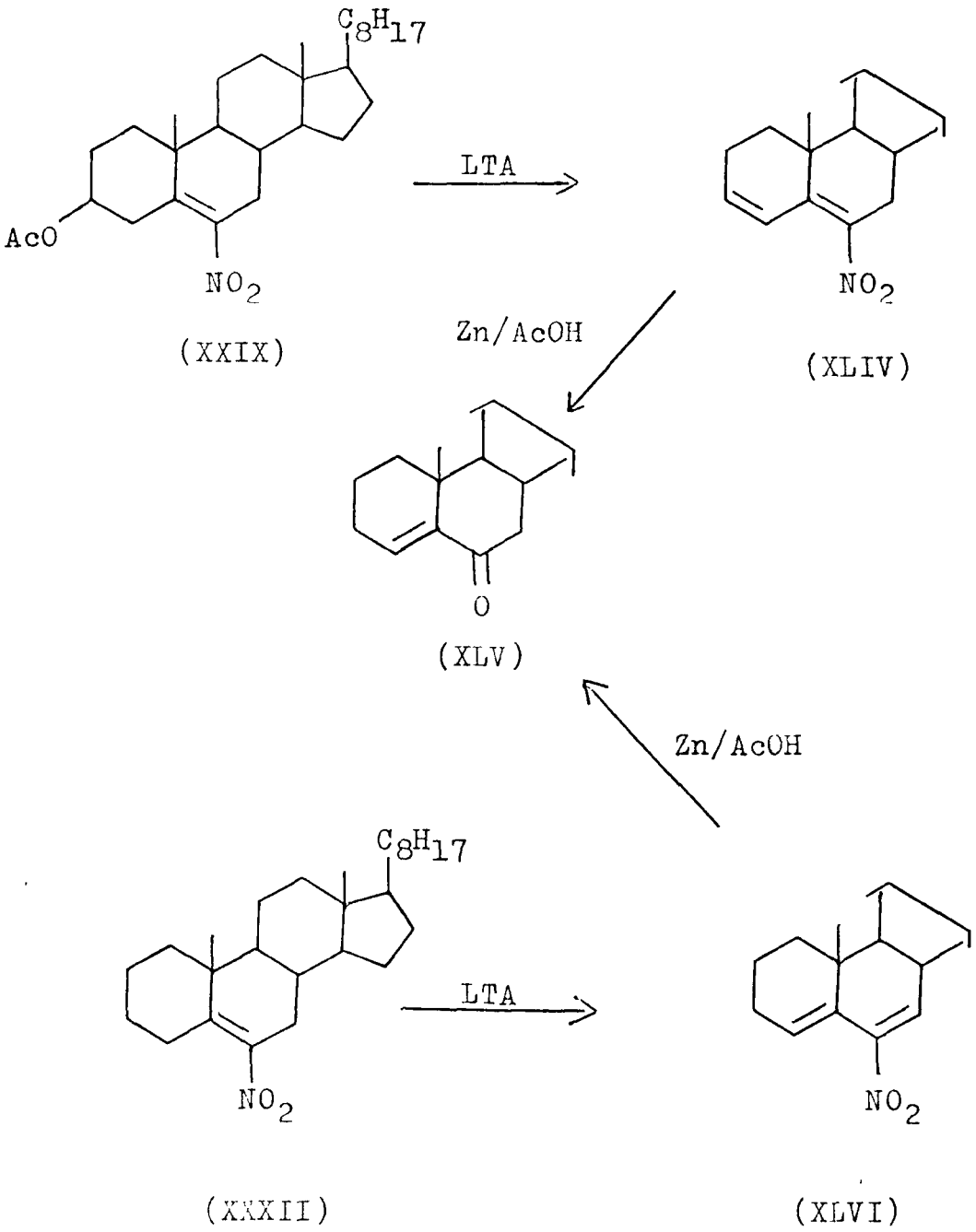
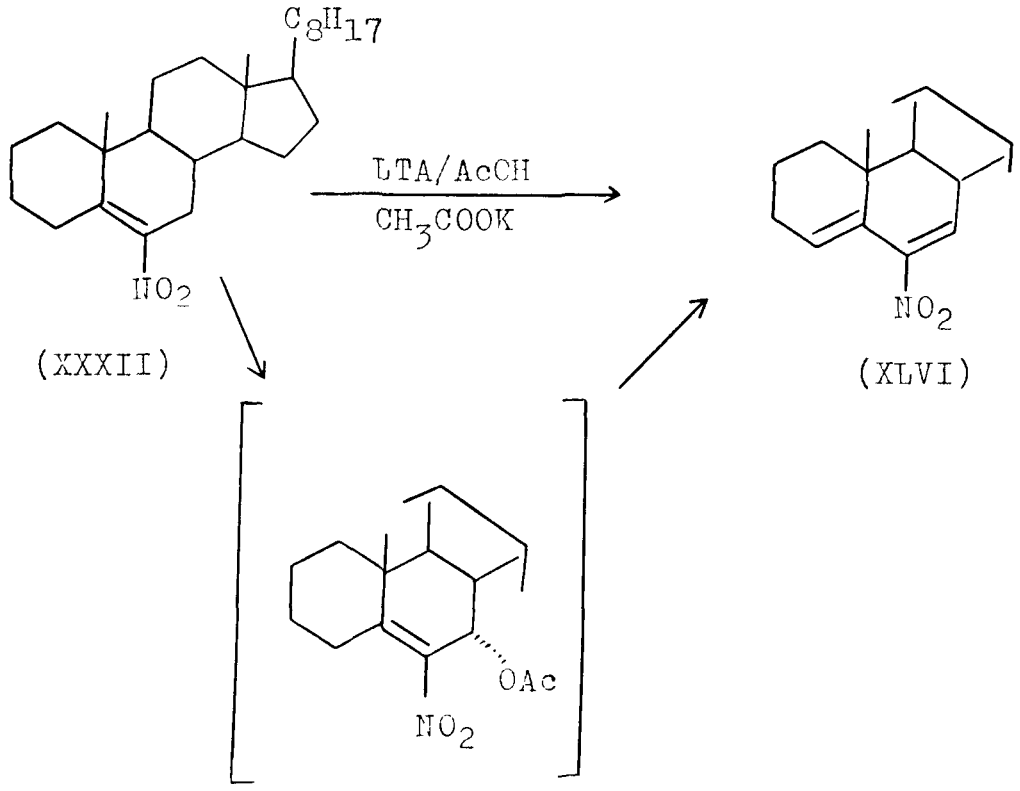
h. Shafiullah, S. Husain and D.H. Basha, Acta Chim. Acad. Sci. (Hung.), 114, 121 (1983).



(XXIX) (XLIV) (XLV) (XXXII) (XLVI)

It is pertinent to mention that no α-acetylation occurred in (XXIX), but lead tetraacetate promoted the elimination of acetic acid to furnish the diene (XLIV). In the case of 6-nitrocholest-5-ene (XXXII) the normal α-acetylated product (XLVII) which could not be isolated, undergoes elimination reaction to furnish the product (XLVI).



SYNTHESIS, CHEMICAL AND SPECTRAL STUDIES OF MODIFIED STEROIDS

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

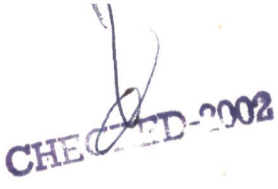
IN

CHEMISTRY

D. MUNAWAR BASHA

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)

1986



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Date 19.12.1986

This is to certify that the work embodied in this thesis entitled, "Synthesis, chemical and spectral studies of modified steroids", is the original work of Mr. D. Munawar Basha carried out under my supervision. The thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

Shafiullah

(SHAFIULLAH)

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(D. MUNAWAR BASHA)

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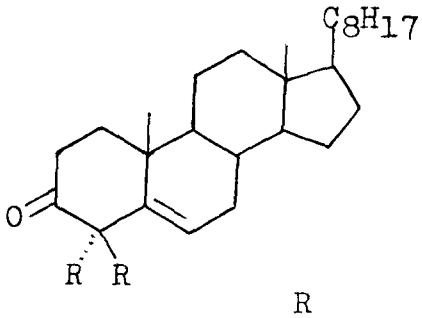
Summary

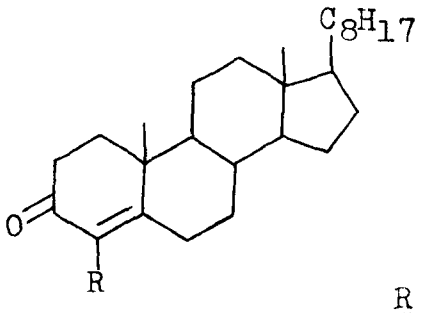
PART ONE

Steroidal Tetrazoles

The physiological properties of the steroidal alkaloids and the discovery of a variety of oxygen and nitrogen containing heterocyclic compounds with useful therapeutic values stimulated extensive research in oxygen and nitrogen containing steroids and this resulted in the preparation of a variety of oxa and aza steroids. The syntheses of steroidal tetrazoles also have become of interest in recent years because of the discovery of biological activity associated with them. Some tetrazoles are used as potential lipolysis inhibitors. A number of steroidal tetrazoles such as (V-IX) which were obtained from ketones (I-IV) were reported from our laboratory.[a]

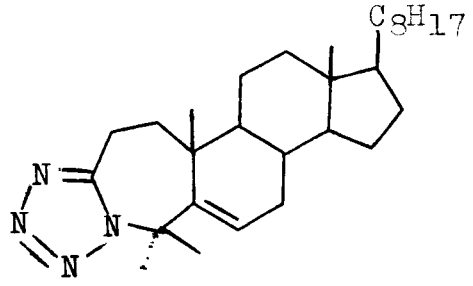


	R
(I)	CH_3
(II)	C_2H_5

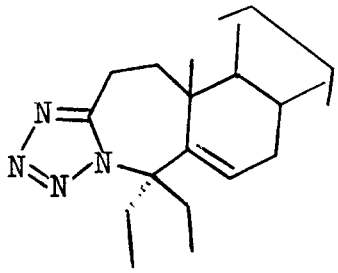


	R
(III)	CH_3
(IV)	C_2H_5

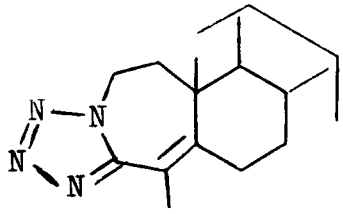
a. Shafiullah and M.A. Gharfari, Acta, Chim. Acad. Sci(Hung.) 103, 333(1980).



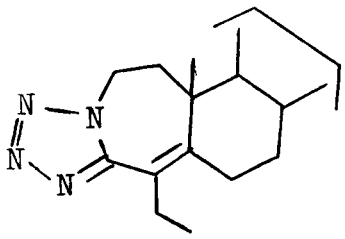
(V)



(VI)



(VII)



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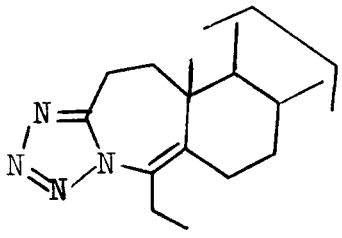
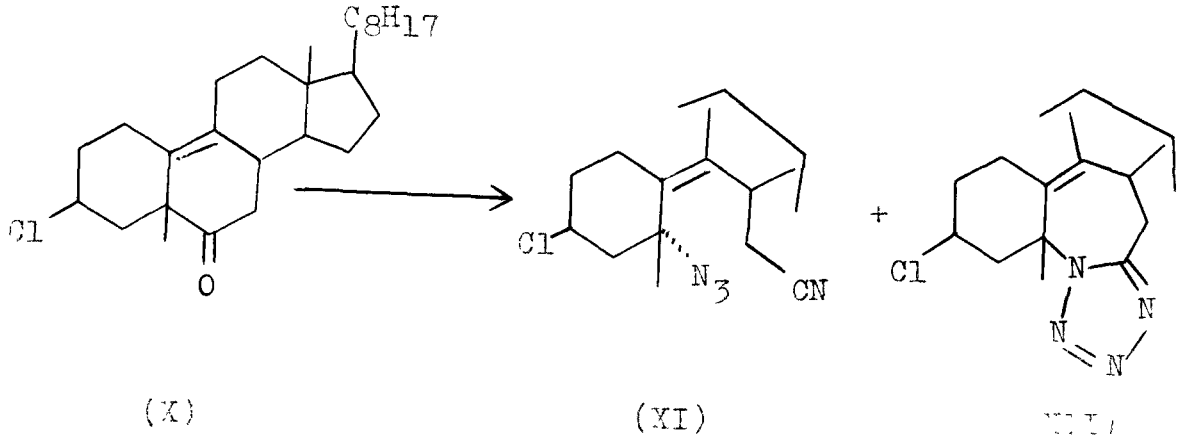
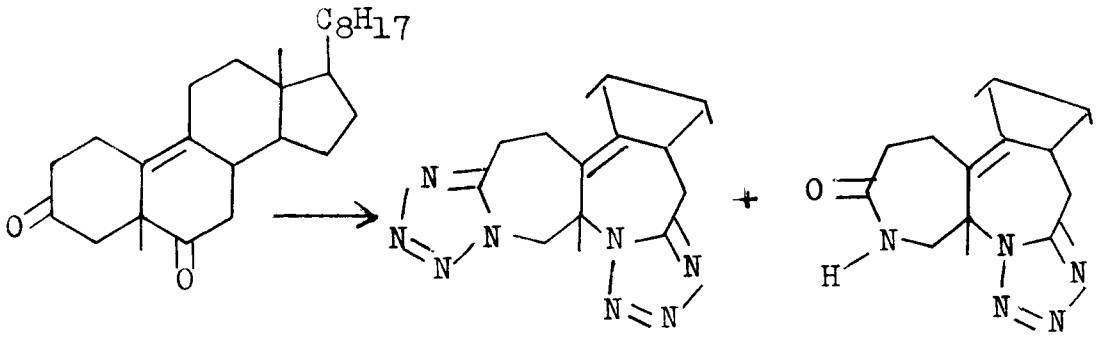


(IX)

The present work is an extension towards the syntheses of steroidal tetrazoles from the less familiar steroidal ketones, 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (X) and 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XIII). The chloroketone (X) when treated with excess of HN_3 (BF_3-etherate as the catalyst) afforded 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (XI) and 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (XII)[b]. The diketone (XIII) under similar reaction conditions furnished 4,6-diaza-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[4,3-d][6,7-d]bistetrazole (XIV) and 4,6-diaza-3-oxo-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (XV). The structures of these compounds were established on the spectral and chemical evidences.



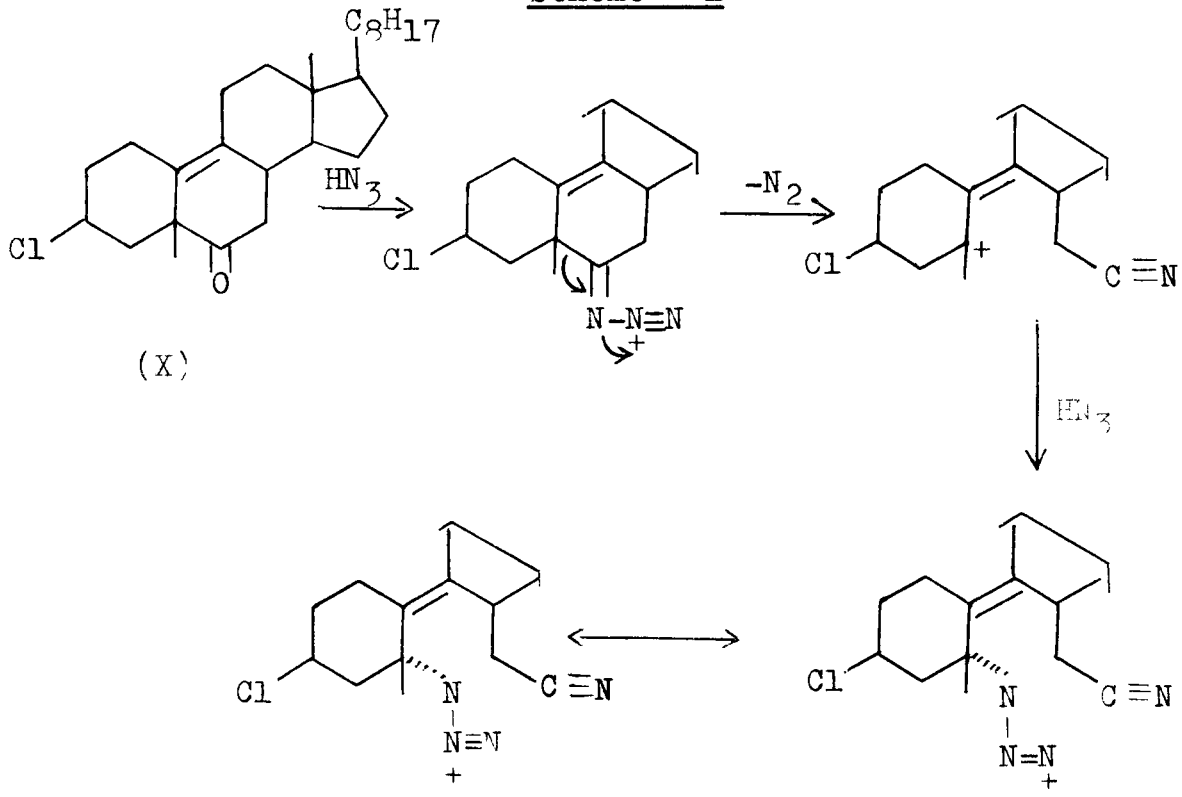
(X) (XI) (XII)



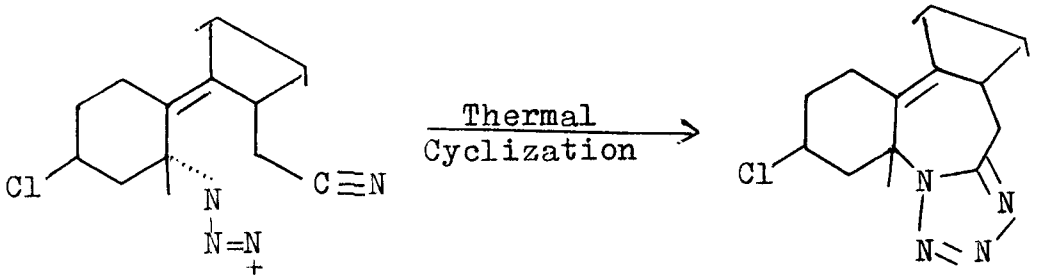
(XIII) (XIV) (XV)

The formation of nitrile (XI), tetrazoles (XII and XIV), and lactamtetrazole (XV) is proposed as follows (Scheme-1 and Scheme-2).

Scheme - 1

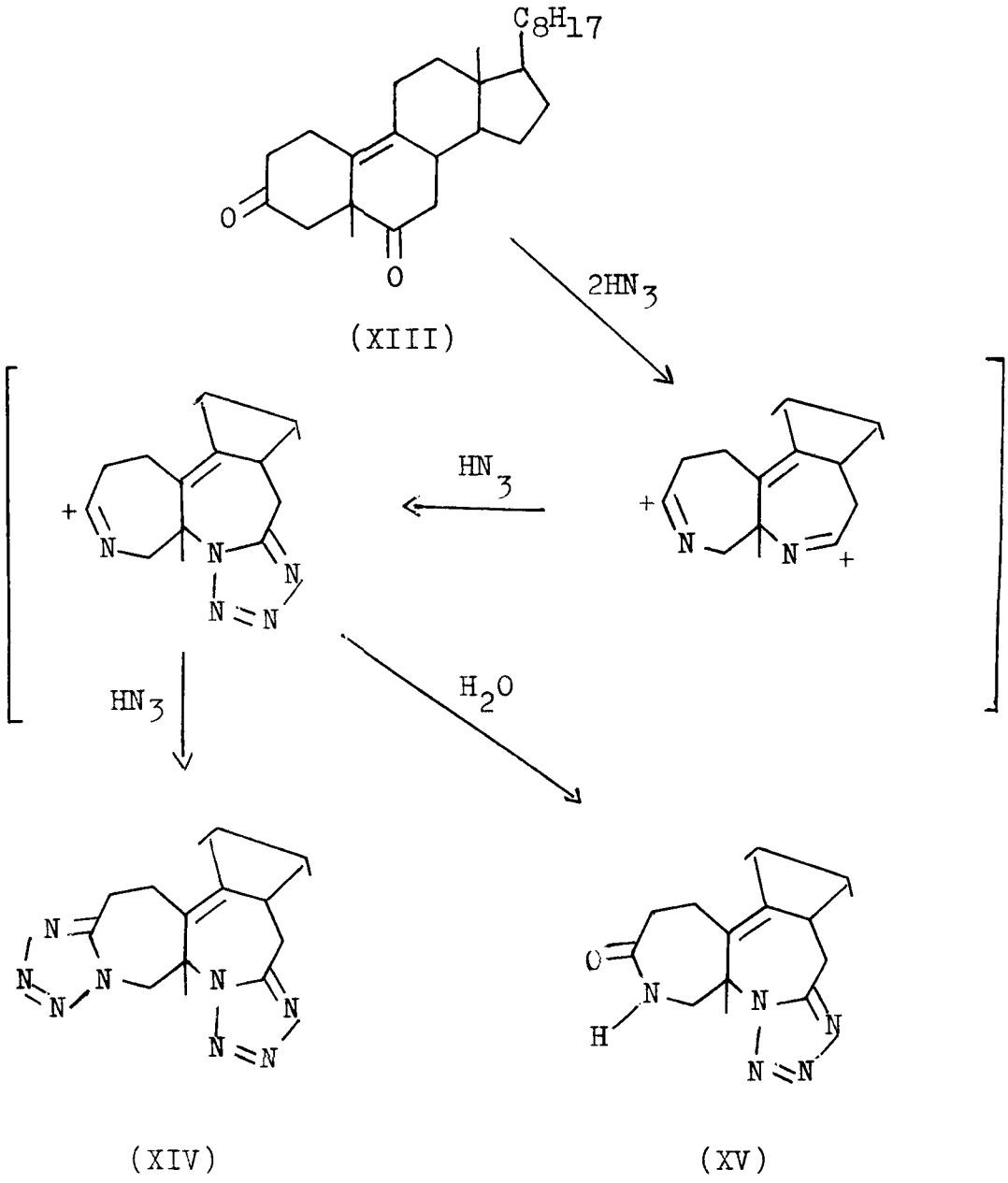


(X) (XI)



(XI) (XII)

Scheme - 2



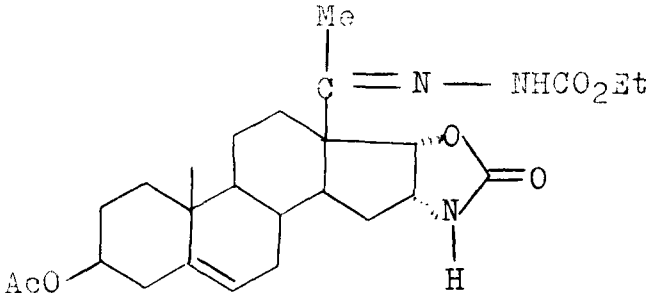
(XIII)

(XIV) (XV)

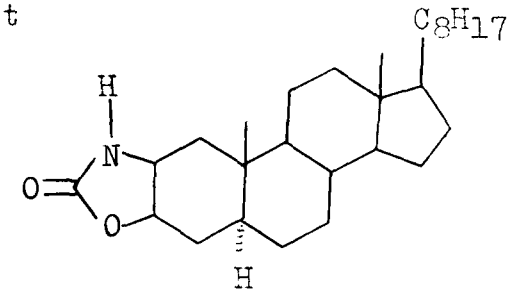
PART TWO

Steroidal Oxazolidinones

Oxazolidinones have been shown to possess various biological activities such as antibacterial, fungicidal, antiinflammatory, herbicidal, analgesic etc. A number of papers appeared describing the various methods for the syntheses of non-steroidal oxazolidinones. The literature survey revealed that no significant work has been done in the field of steroidal oxazolidinones and only a few oxazolidinones such as (XVI)[b] and (XVII)[c] have been reported



(XVI)



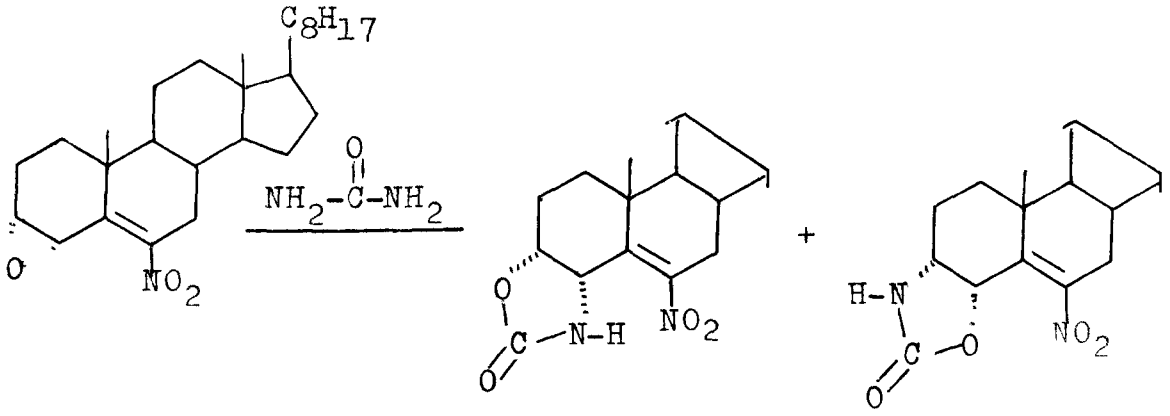
(XVII)

b. Z.I. Istomina and A.M. Turuta, Chem. Abstr., 92, 147038 (1980).

c. A.J. Jones, P.F. Alewood, M. Benn and J. Wong, Tetrahedron Lett. 1655 (1976).

This prompted us to synthesise steroidal oxazolidinones from a recently reported[d] epoxide, 3α,4α-epoxy-6-nitrocholest-5-ene (XVIII) by the reaction of urea and also of acetamide.

The epoxide (XVIII) in N,N-dimethyl formamide when refluxed with urea gave after column chromatography over silica gel 6-nitrocholest-5-eno[4α,3α-d]oxazolidin-2'-one (XIX) and 6-nitrocholest-5-eno[3α,4α-d]oxazolidin-2'-one (XX). Under identical reaction conditions the epoxide (XVIII) with acetamide provided 6-nitrocholesta-3,5-diene (XXI), 3α,4β-dihydroxy-6-nitrocholest-5-ene (XXII) and oxazolidinone (XX). Stereochemical study for the characterization of epimeric oxazolidinones (XIX) and (XX) was done with the help of NMR spectroscopy. A mechanism was also suggested for their formation.



(XVIII) (XIX) (XX)

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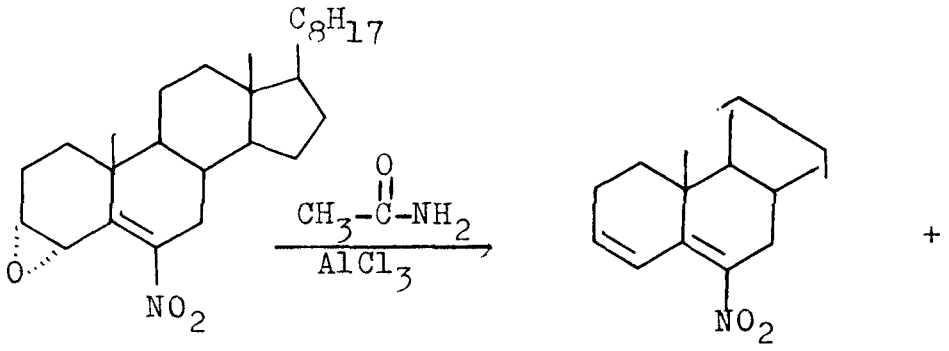
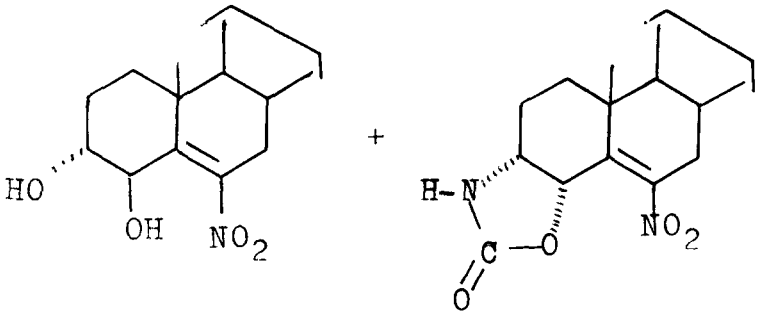
d. Shafiul Hah, Shakir Husain and M. Rafiuddin Ansari, Ind. J. Chem., 24B, 662 (1985).



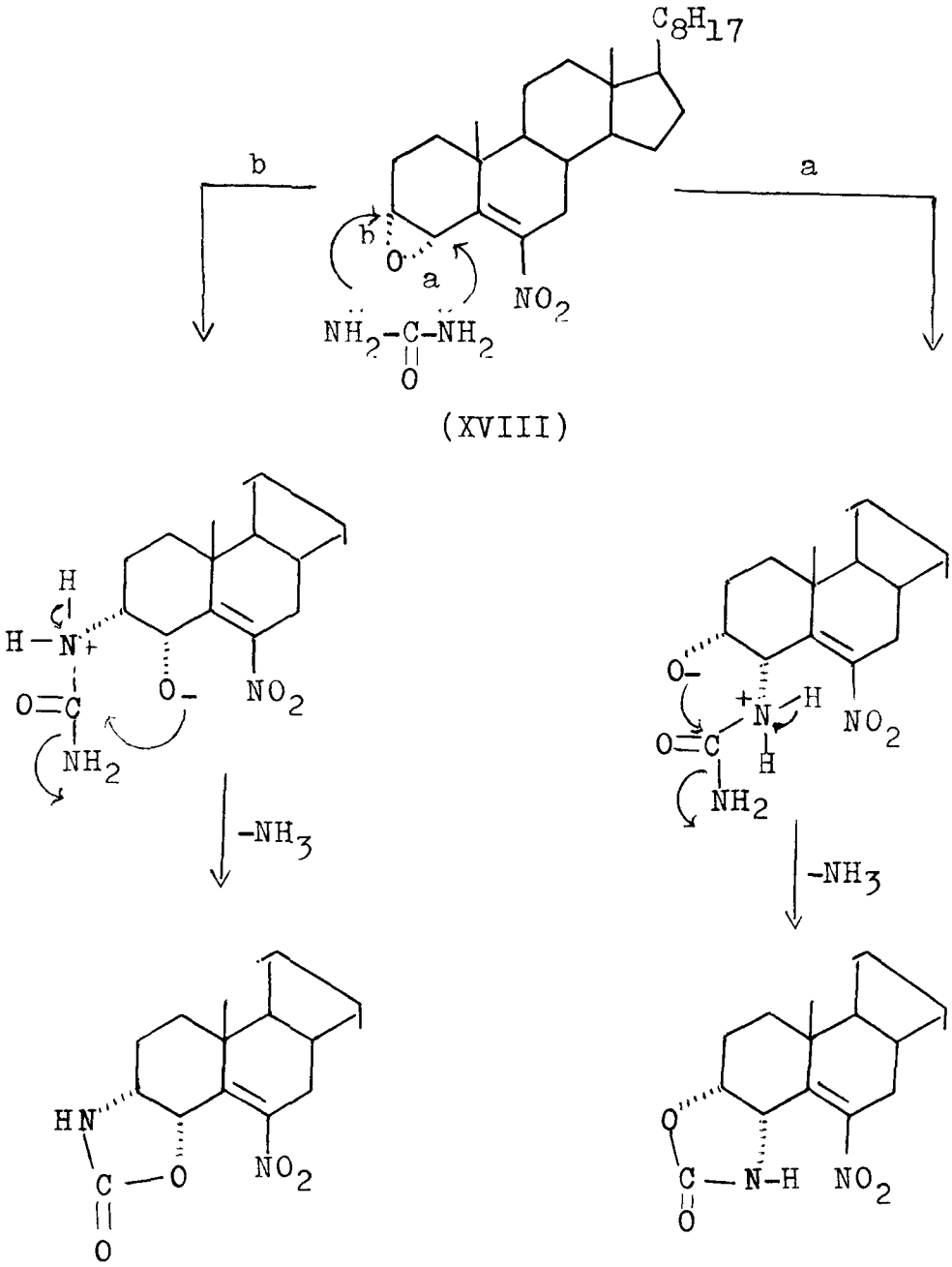
(XVIII) (XXI)



(XXII) (XX)

Formation of the isomeric oxazolidinones (XIX) and (XX) from the epoxide (XVIII) by the reaction of urea may be explained by the following tentative mechanism (Scheme-3).

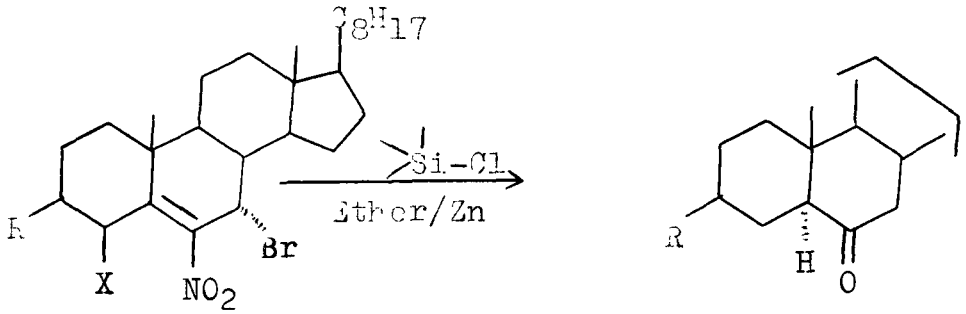
Scheme - 3



PART THREE

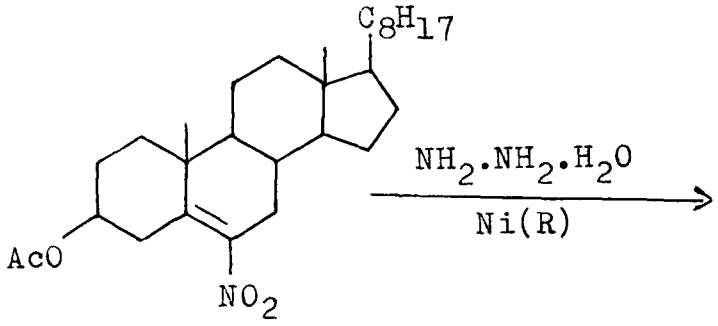
Reduction of Steroidal Nitroolefins

Reduction is one among the various reactions used in the synthetic pathway in Organic Chemistry. Many types of reagents were successfully employed for this purpose. Recently in our laboratory chlorotrimethylsilane was used to reduce the steroidal nitroolefins (XXIII, XXIV and XXV) to the corresponding ketones (XXVI, XXVII and XXVIII)[e] at room temperature, to make use of the utility of the reagent. In present work, reduction with hydrazine-hydrate, catalysed by Raney nickel was carried out to impress upon the utility, in the syntheses of steroidal compounds. 3β-Acetoxy-6-nitrocholest-5-ene (XXIX) provided 3β-acetoxy-5α-cholestan-6-one (XXVI), 3β-acetoxy-5α-cholestan-6-one oxime (XXX) and 3β-hydroxy-5α-cholestan-6-one (XXXI) under the reduction conditions.

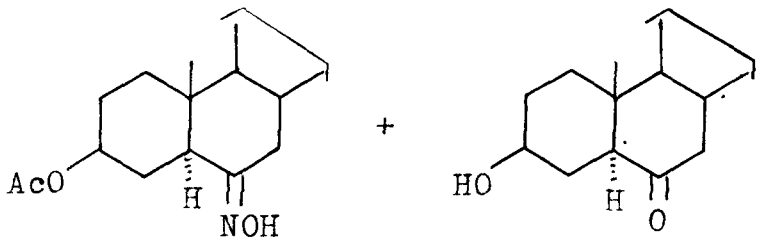


	A	X		R
(XXIII)	OAc	H	(XXVI)	OAc
(XXIV)	Cl	H	(XXVII)	Cl
(XXV)	H	Br	(XXVIII)	H

e. Shafiullah and Shakir Husain, J. Ind. Chem. Soc., 62, 163 (1985).

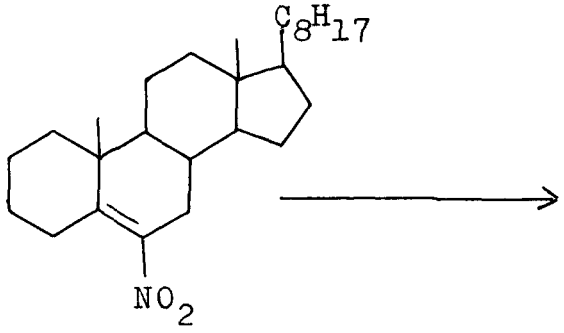


(XXIX) (XXVI)

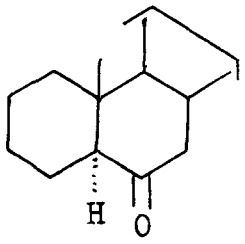


(XXX) (XXXI)

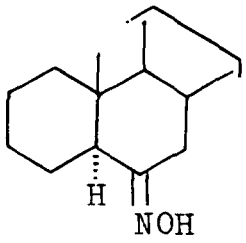
When 6-nitrocholest-5-ene (XXXII) was reduced gave the usual products, ketone and oxime (XXVIII and XXXIII) along with 6β-amino-5α-cholestane (XXXIV). Reduction of 3β-chloro-6-nitrocholest-5-ene (XXXV) gave 3β-chloro-5α-cholest-6-one (XXVII)the usual product, along with two dimers,3β,3'β-dichloro-5α,5'α-6,6'-bisazocholestane (XXXVI) and 3α,5α-3'α-5'α-cyclo-6,6'-bisazocholestane (XXXVII).



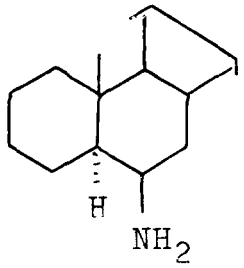
(XXXII)



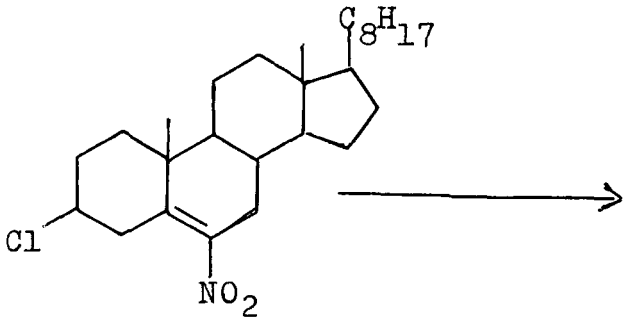
(XXVIII)



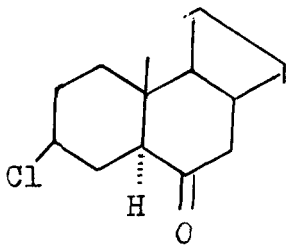
(XXXIII)



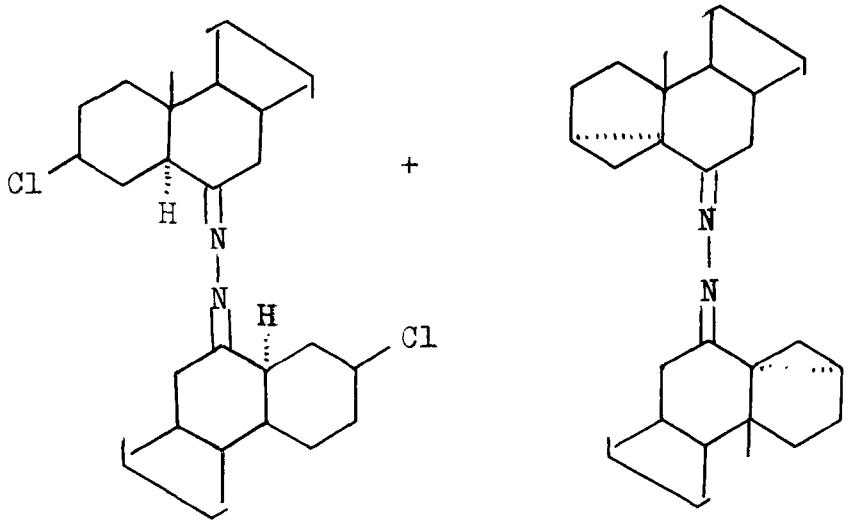
(XXXIV)



(XXXV)

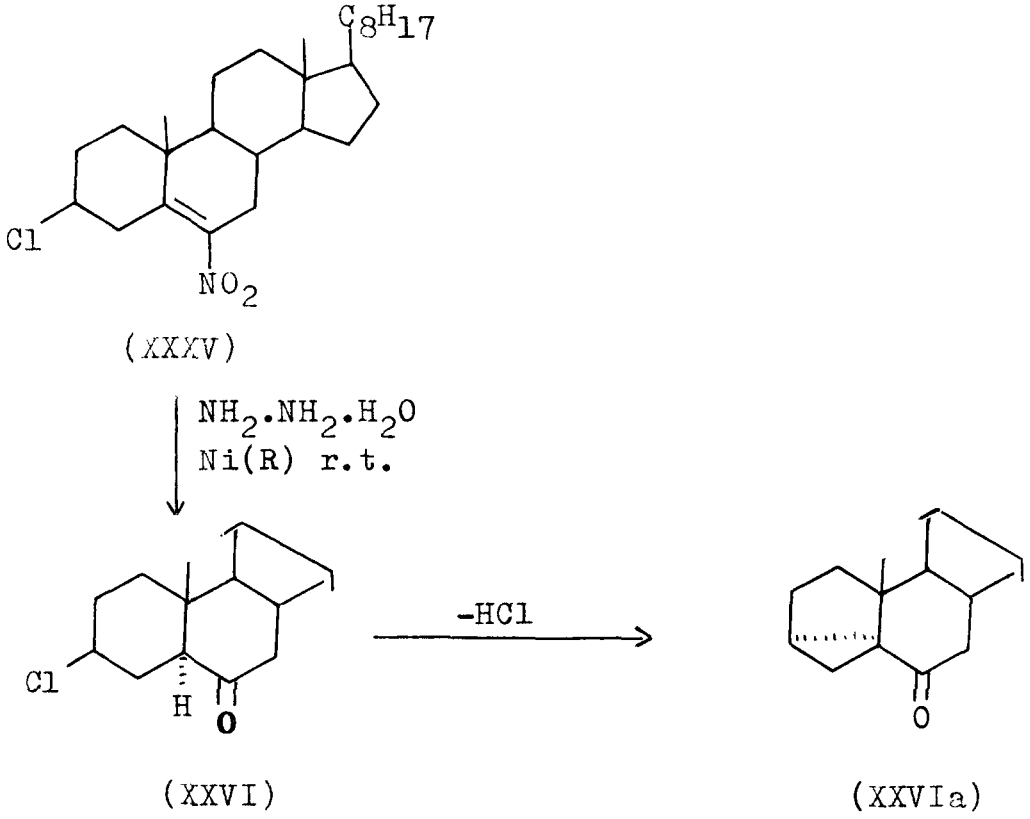


(XXVII)



(XXXVI) (XXXVII)

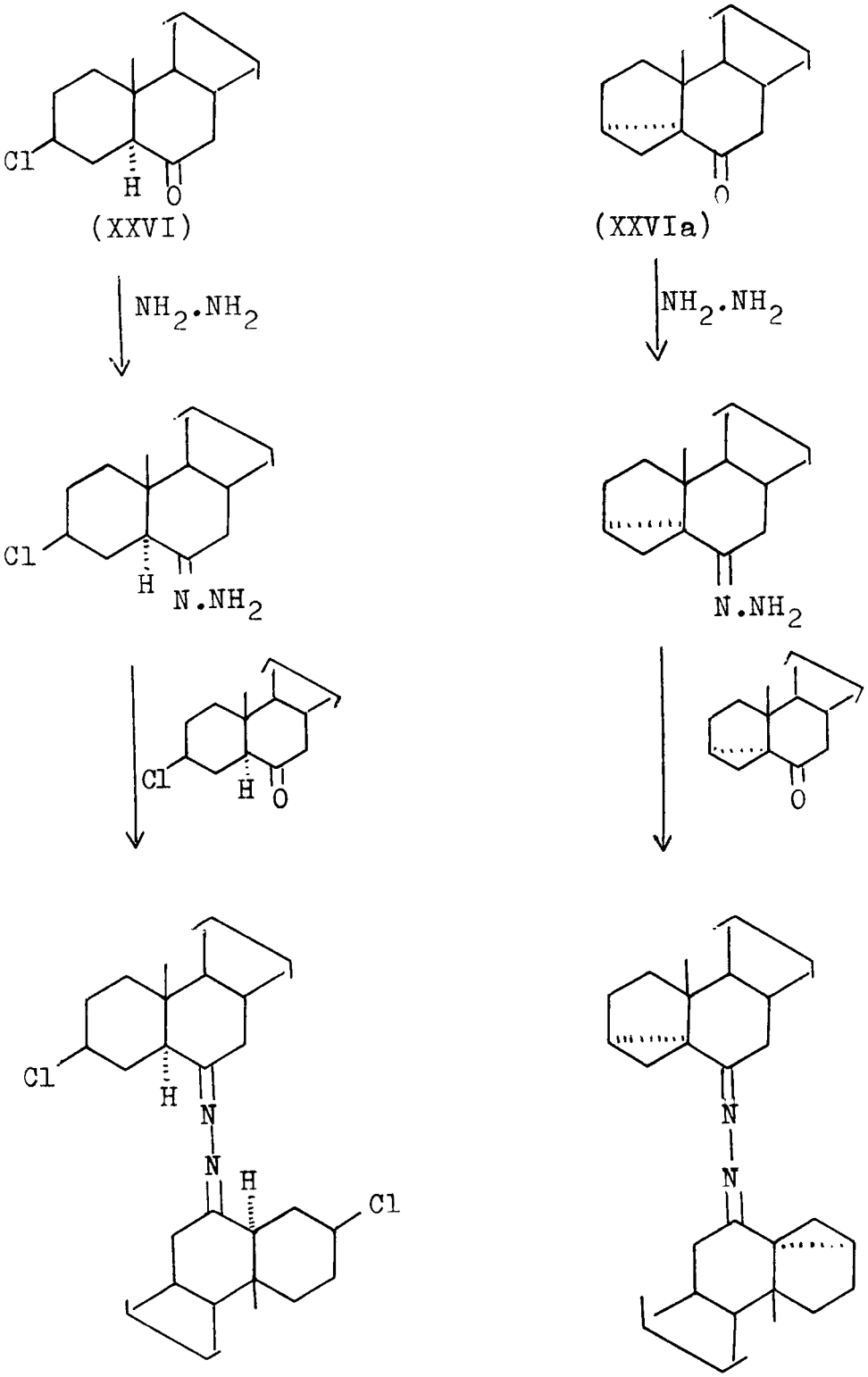
A tentative mechanism is proposed to explain the formation of the dimers (XXXVI and XXXVII) in which the ketones (XXVI and XXVIa) formed, react with hydrazine to furnish the corresponding dimers (Scheme - 4).



(XXXV)

(XXVI) (XXVIa)

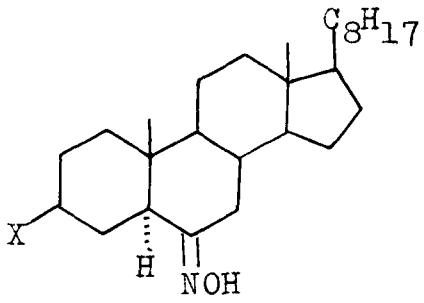
Scheme - 4


Cl
H
O
(XXVI)
$NH_2.NH_2$
Cl
H
N.NH_2
Cl
H
O
Cl
H
N
N
H
Cl
(XXXVI)
O
(XXVIa)
$NH_2.NH_2$
N.NH_2
O
N
N
(XXXVII)

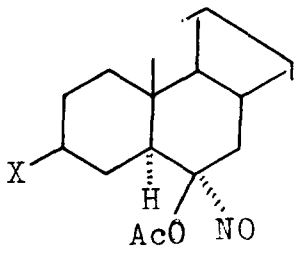
PART FOUR

Oxidation of Steroidal-6-nitroolefins with Lead Tetraacetate

Lead tetraacetate in glacial acetic acid reacts with simple alkenes, ketones, oximes, alcohols and lactones and provides a variety of products. Previous work[f,g] from our laboratory described the reaction of lead tetraacetate on steroidal oximes (XXXVIII) and interesting products such as steroidal nitrosoacetates (XXXIX) and nitroacetate (XL) were reported. In continuation to it we carried out the lead tetraacetate oxidation of steroidal nitroolefins about which no mention has been made in the literature.

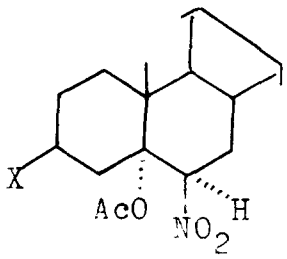


(XXXVIII)



(XXXIX)

+



(XL)

X = H, OH, OAc, Cl, Br, I.

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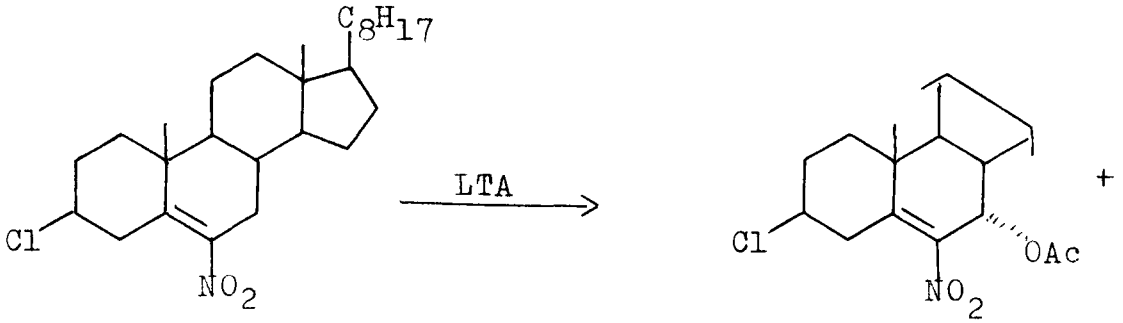
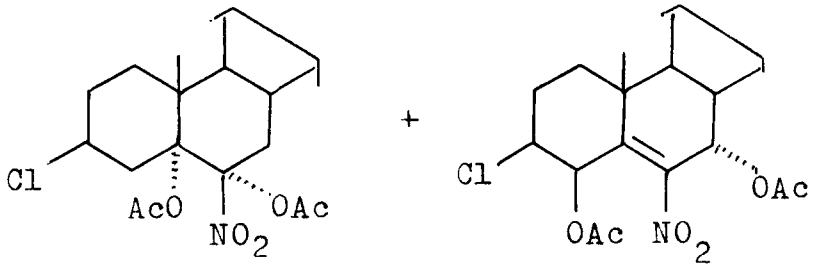
f. Shafiullah and Hasrat Ali, Synthesis, 124 (1979).

g. Shafiullah, Hasrat Ali and Shamsuzzaman, Acta. Chim. Acad. Sci. (Hung.) 107, 97 (1981).

The reaction of 3β-chloro-6-nitrocholest-5-ene (XXXV) provided the α-acetylated products (XLI and XLII) and also an addition product (XLIII)[h] where as the reaction of 3β-acetoxy-6-nitrocholest-5-ene (XXIX) and 6-nitrocholest-5-ene (XXXII) provided the conjugated nitroolefins (XLIV and XLVI) respectively. The products are characterized on the basis of their spectral and chemical studies.



(XXXV) (XLI)



(XLII) (XLII)

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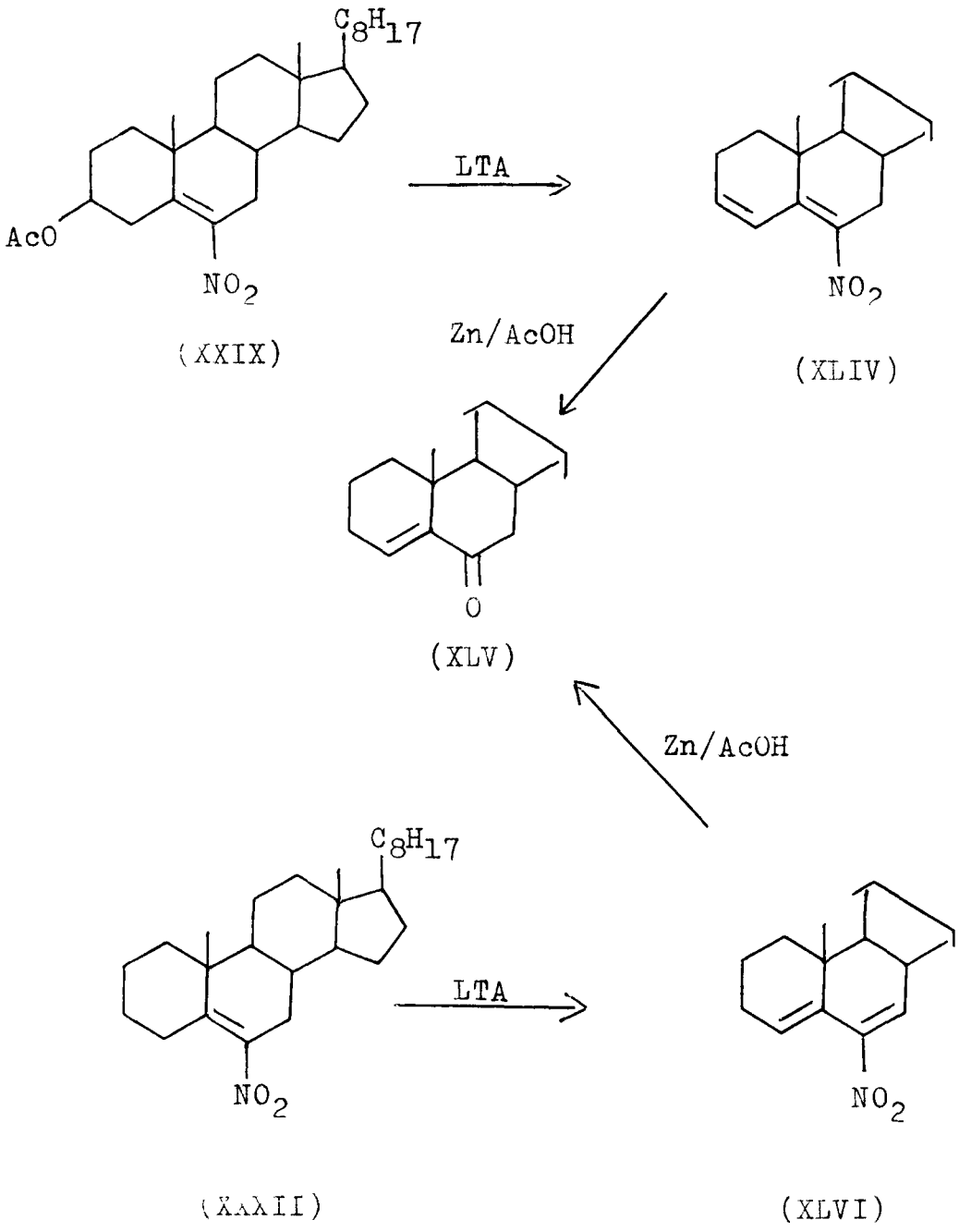
h. Shafiullah, S. Husain and D.M. Basha, Acta Chim. Acad. Sci. (Hung.), 114, 121 (1983).



(XXIX)

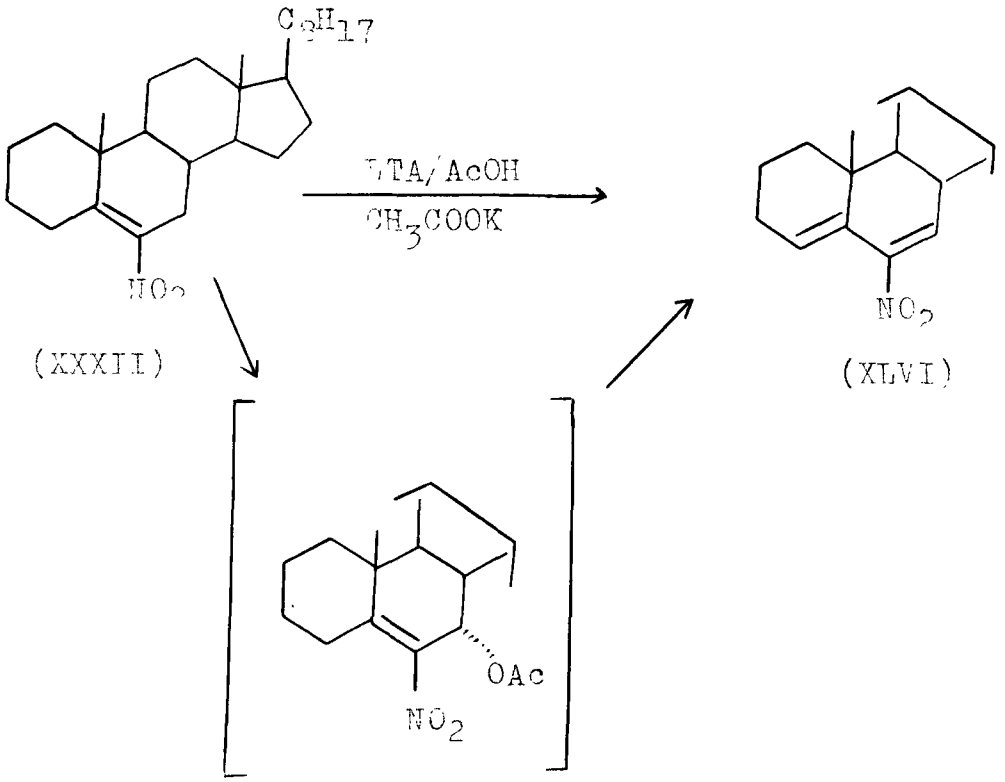
(XLIV)

(XLV)

(XXXII)

(XLVI)

It is pertinent to mention that no α-acetylation occurred in (XXIX), but lead tetraacetate promoted the elimination of acetic acid to furnish the diene (XLIV). In the case of 6-nitrocholest-5-ene (XXXII) the normal α-acetylated product (XLVII) which could not be isolated, undergoes elimination reaction to furnish the product (XLVI).



(XXXII) (XLVI)

(XLVII)

Introduction

For the past fifty years the chemistry of steroids has provided one of the most interesting and thoroughly explored area for organic chemists. The dramatic expansion of steroidal chemistry came with the discovery of steroidal hormones. The discovery of several biologically active steroids with their wide application in therapy have brought about an increasing interest. The synthetic modification of naturally occurring steroids with the hope of improving pharmacological essentialities has resulted in the preparation and discovery of a number of diverse pharmacologically active, potent, highly specific commercially important therapeutic agents. The physiological activity of steroidal hormones depends on a number of factors. Among those of primary importance are stereochemistry and overall shape of the molecule. Even a fundamental change (introduction of double bond, hydroxy group, acetate group, ring enlargement and contraction etc.) in the steroid skeleton should alter the stereochemistry at least to some extent. Thus during the last decade the major efforts of the chemists were directed towards the modification in the structure of steroid in order to enhance their non-hormonal activity and to increase the selectivity of certain biologically active compounds. Our laboratory, concerned mainly with the syntheses of steroidal

compounds and their identification by chemical and spectral studies, has reported the preparation of a number of hetero-steroids.

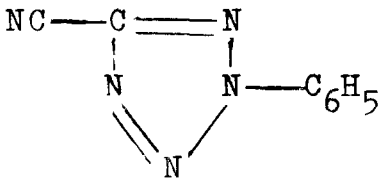
In the present work an attempt has been made to synthesize some modified steroids of biological interest such as tetrazoles and oxazolidinones. One of the chapters covers the Raney nickel catalysed reduction of steroidal nitroolefins and the final chapter is on oxidation of steroidal nitroolefins. In some cases along with the usual products, abnormal products have also been obtained which has offered scope for some mechanistic and stereo-chemical studies too.

Part One

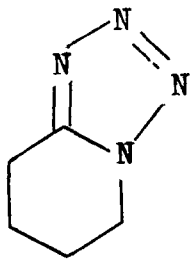
Steroidal Tetrazoles

Theoretical

Tetrazoles are a class of heterocyclic compounds containing four nitrogen atoms and one carbon atom arranged in a fashion to constitute a five membered ring with two alternate double bonds. Bladin[1,2] reported the first tetrazole (I) formed by the treatment of dicycanophenyl hydrazine with nitrous acid. Tetrazoles have found various biological as well as non-biological applications. Pentamethylene tetrazole (II) is a potent stimulant of the central nervous system and is used clinically to counter act intoxication due to overdosage of barbiturates[3].



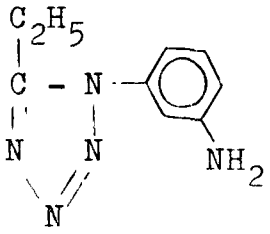
(I)



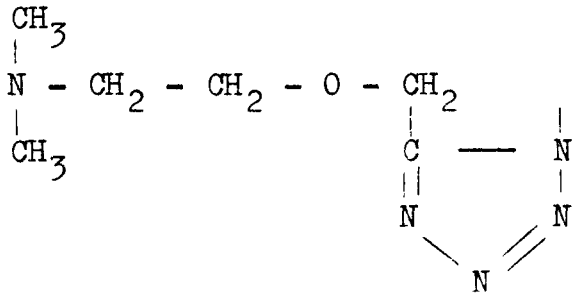
(II)

Stimulant and depressant effects are exhibited by disubstituted tetrazoles carrying alkyl, cycloalkyl, aryl, amino and amide groups[4-7]. Analgesic and sedative activities are shown by 5-monosubstituted tetrazoles[8]. Anticonvulsant activity in mice is exhibited by 1-(m-aminophenyl)-5-ethyltetrazole (III). Hypotensive activity is found in 5-(2-dimethylaminoethoxymethyl)-1-phenyltetrazole (IV), the effect being directly on cardiac and

vascular muscle[9]. Various biological activities such as anti-allergic[10], anticonvulsant[11], antiulcer[12], antibacterial[13], antiviral[13], antifungal[13], antiinflammatory[14], analgesic[15] and antihypertensive[16] have been recently reported for tetrazoles. Tetrazoles have been applied in explosives and in propellants. Tetracene[17] has been used as an initiator. Applications in photography[18,19] have also been reported.



(III)

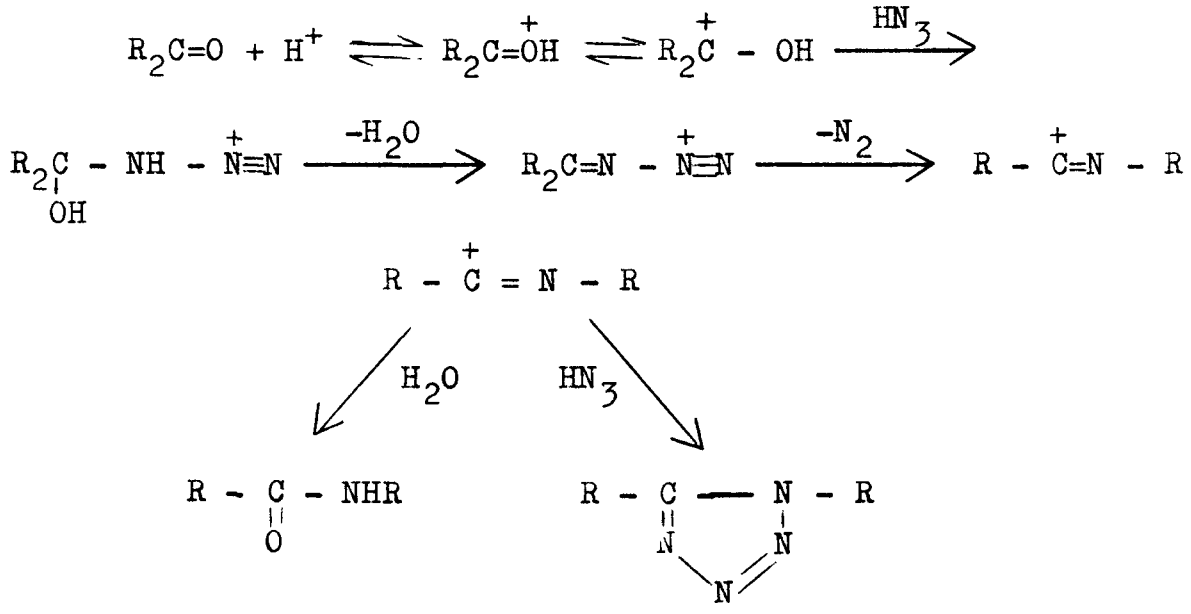


(IV)

Tetrazoles were formed by (i) addition of hydrazoic acid to compounds with carbon-nitrogen unsaturation, such as nitriles, cyanates, thiocyanates, isocyanates, cyanamides, carbamides and isothiocyanates, (ii) displacement reaction between imide chloride and hydrazoic acid, (iii) hydrazine-nitrite reaction, (iv) acyl-hydrazine diazonium reaction, (v) hydrazone-azide reaction and (vi) rearrangement. One of the most valuable methods for the preparation of 1,5-disubstited tetrazole is the reaction between ketones and hydrazoic acid in the presence of strong acids, a slight modification of Schmidt reaction[20]. The reaction has found its extensive applications with cyclic ketones with which

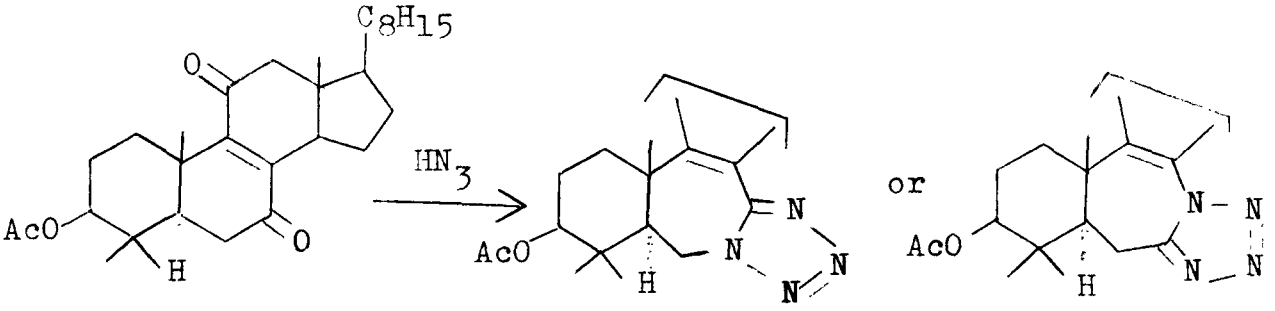
yields were generally better than with acylic ketones.

Smith[21] has given suitable mechanism for the Schmidt reaction. The first step is the conversion of carbonyl compound to a carbonium ion under the influence of the acid catalyst. This is followed by combination with one molecule of hydrazoic acid (functioning as a base), dehydration of the intermediate and rearrangement of an iminocarbonium ion, with simultaneous loss of nitrogen. When tetrazole forms, a second molecule of hydrazoic acid reacts with the iminocarbonium ion, the positive charge being lost as a hydrogen ion. There is competition between hydrazoic acid and water molecule to combine with the iminocarbonium ion to form a tetrazole or an amide respectively.

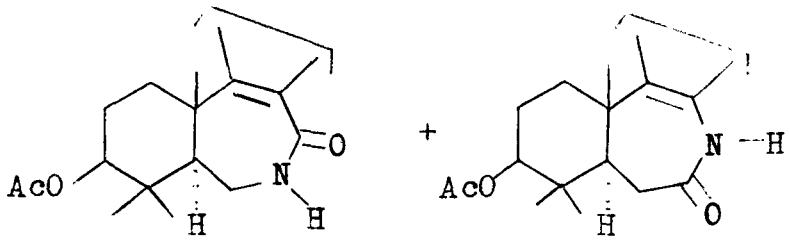


Barnes et al.[22] were the first to report the formation of tetrazole in steroid and triterpenoid systems. Treatment of

7,11-dioxolanost-8-en-3β-yl acetate (V) with hydrazoic acid yielded a tetrazole (VIa or VIb) in addition to two isomeric monolactams (VII and VIII).

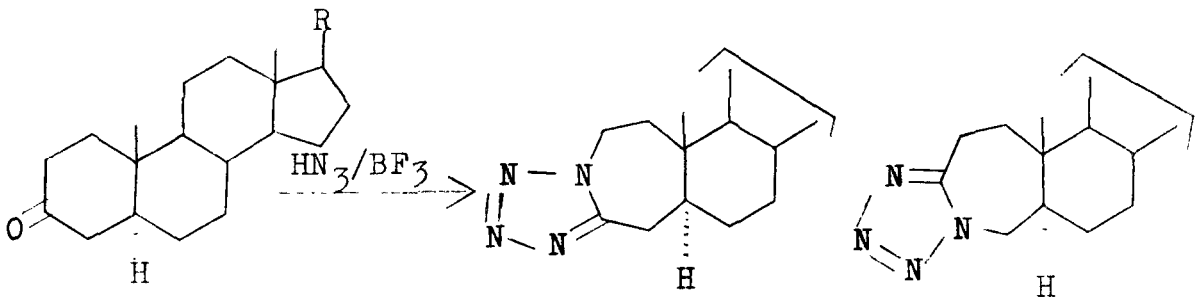


(V) (VIa) (VIb)



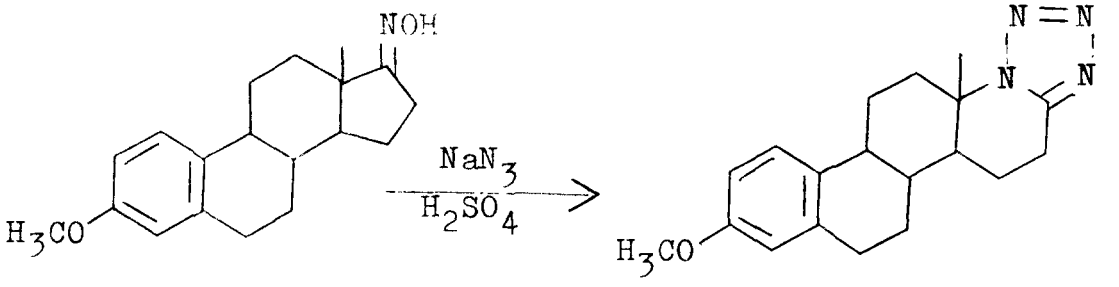
(VII) (VIII)

Biologically active steroidal tetrazoles were reported by Mechoulam[23]. When 5α-cholestan-3-one (IX) and 17β-hydroxy-5α-androstan-3-one (X) were subjected to Schmidt reaction, isomeric tetrazoles (XI-XIV) were obtained.

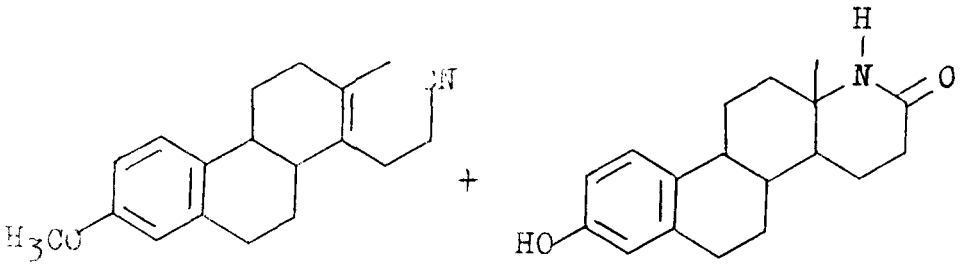


	R		R		R
(IX)	C_8H_{17}	(XI)	C_8H_{17}	(XII)	C_8H_{17}
(X)	OH	(XIII)	OH	(XIV)	OH

Cervantes et al.[24] reported the formation of ring-D fused tetrazole (XVI) from the reaction of 17-ketoxime (XV) with an excess of sodium azide in the presence of H_2SO_4. The formation of nitrile (XVII) and lactam (XVIII) was also reported.

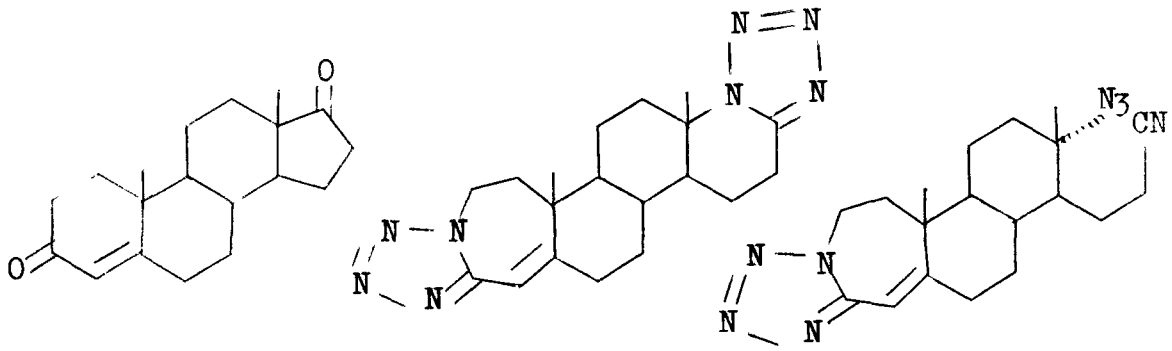


(XV) (XVI)



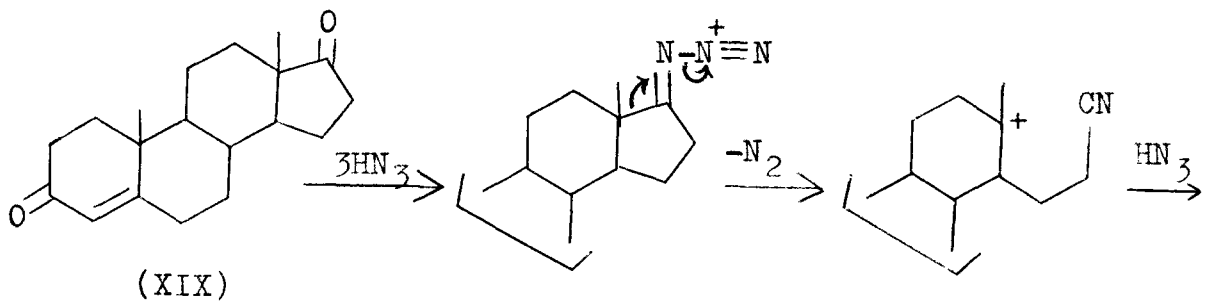
(XVII) (XVIII)

Singh et al.[25,26] have reported that androst-4-ene-3,17-dione (XIX) on treatment with excess of hydrazoic acid - BF_3-etherate in chloroform yielded the expected 3,17a-diaza-A,D-bishomoandrost-4a-eno[3,4-d][17a,17-d]bistetrazole (XX) and an unusual product, 13,17-seco-13α-azido-3-aza-A-homoandrost-4a-eno [3,4-d]tetrazol--17-nitrile (XXI). The azido nitrile cyclized on heating to give (XX).

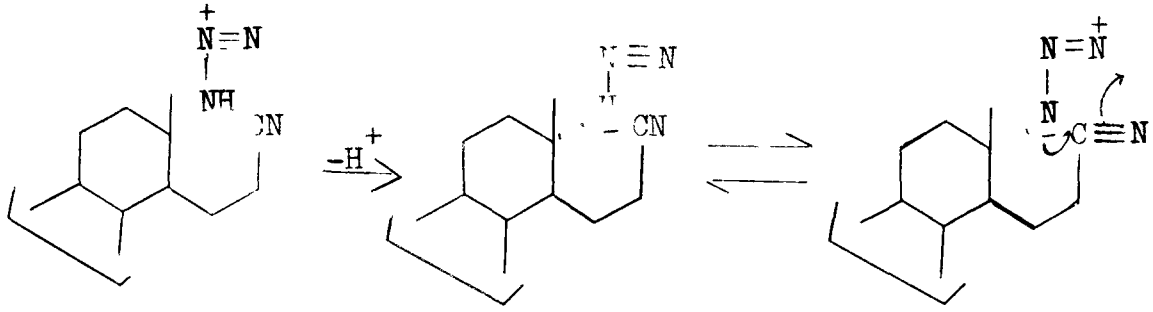


(XIX) (XX) (XXI)

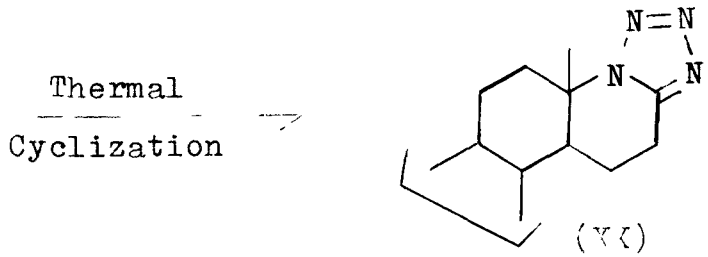
To account for this novel cleavage of 17-oxosteroid (XIX) to azido nitrile (XXI) and its subsequent cyclization to tetrazole (XX) the following mechanism was proposed.



(XIX)

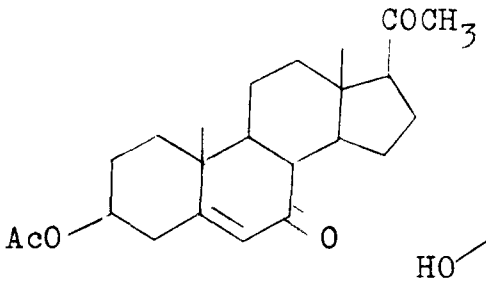


(XXI)

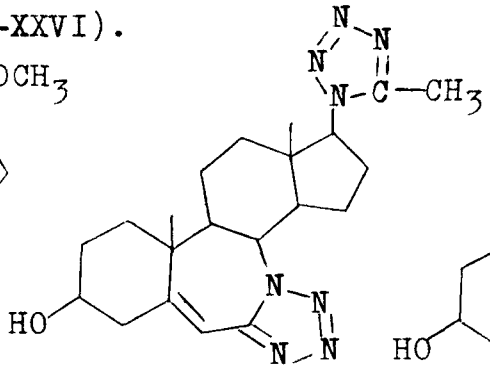


(XX)

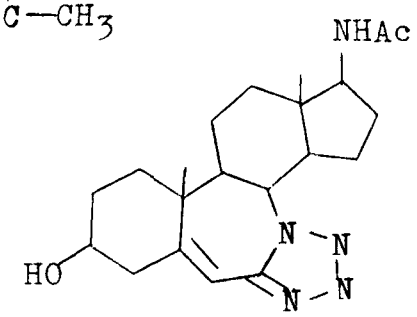
When 3β-acetoxypregn-5-ene-7,20-dione (XXII) was treated with hydrazoic acid - BF_3-etherate in chloroform yielded[27] 17β-(5-methyltetrazole-1-yl)-7a-aza-B-homoandrost-5-eno[7a,7-d] tetrazol-3β-ol (XXIII) as major product followed by other tetrazoles (XXIV-XXVI).



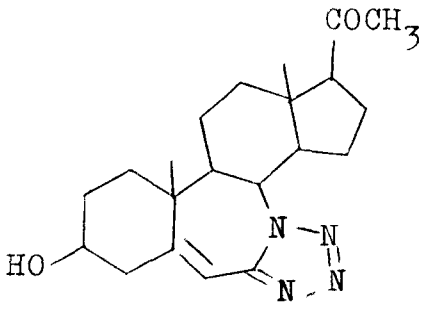
(XXII)



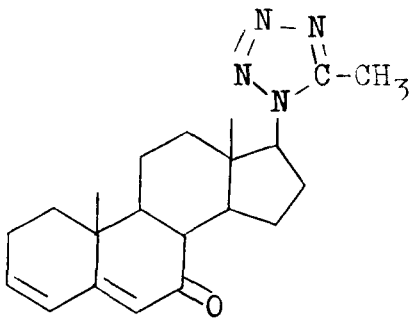
(XXIII)



(XXIV)

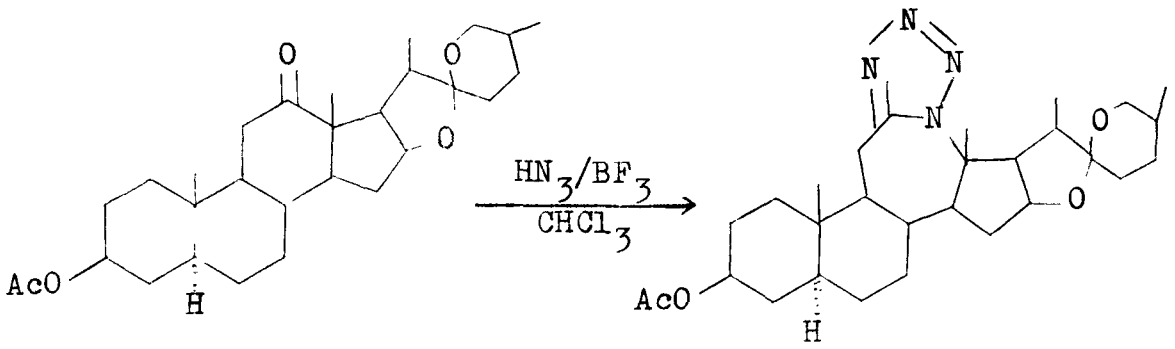


(XXV)



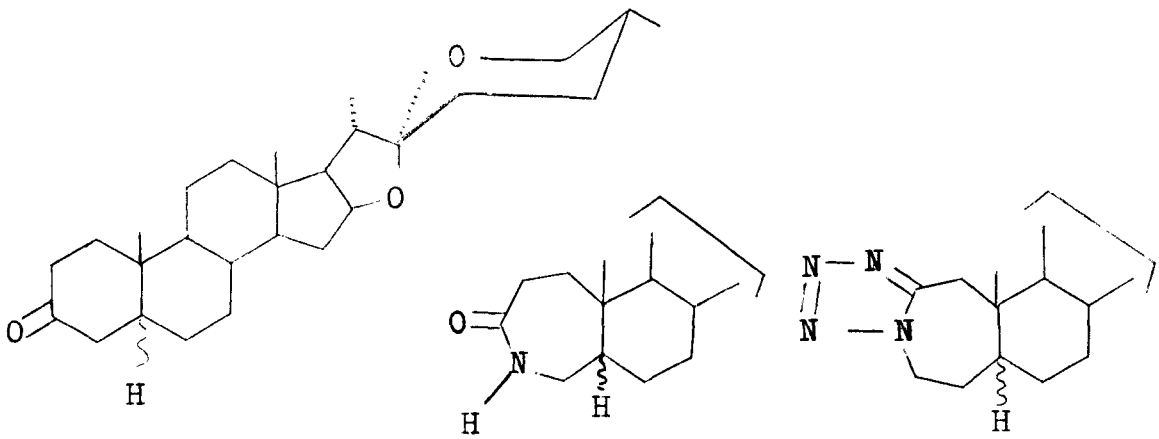
(XXVI)

Ring-C fused tetrazole (XXVIII) was reported[28] through a similar reaction from (XXVII). Various steroidal tetrazoles have been reported[29,30] to be formed by the action of excess of hydrazoic acid with 6-oxo and 7-oxo steroidal compounds. In most of the cases lactams have been reported as one of the products.



(XXVII) (XXVIII)

Irismetov et al.[31] reported that Schmidt reaction of 5α- and 5β-spirostanones (XXIX) gave the lactams (XXX) and tetrazolospirostanes(XXXI).

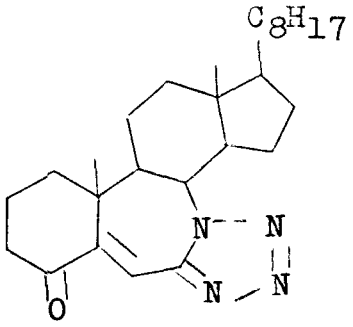
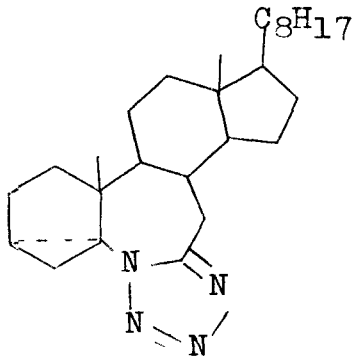


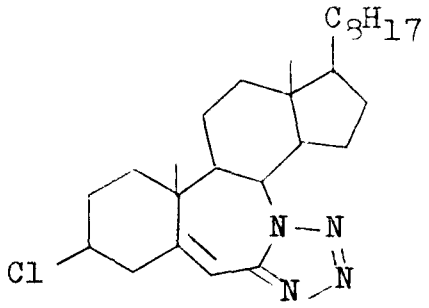
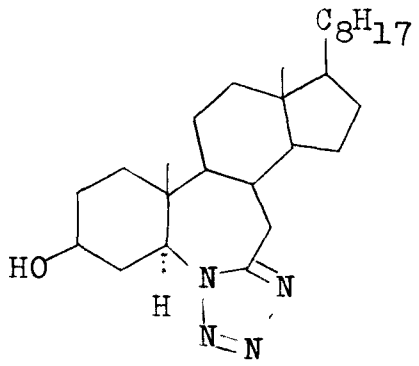
(XXIX) (XXX) (XXXI)

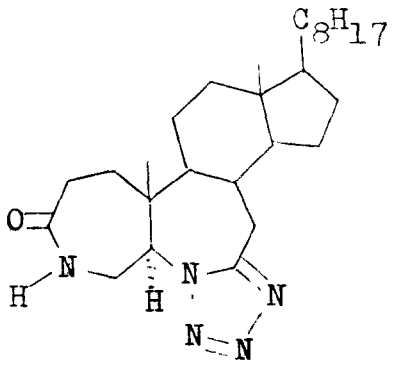
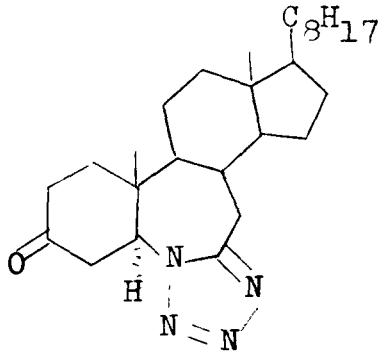
A large number of tetrazoles reported from our laboratory in the last few years are tabulated along with their spectral data (Table - 1).

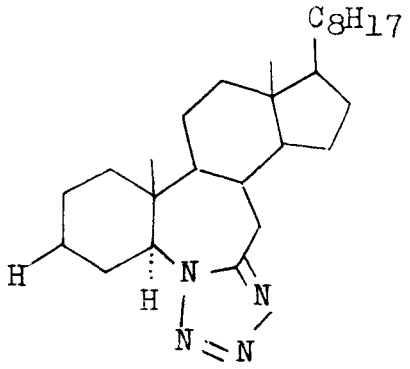
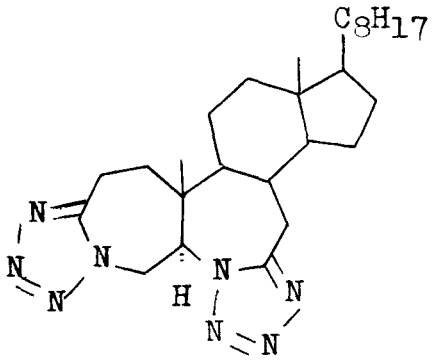
TABLE - 1

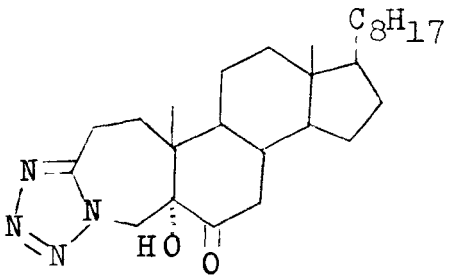
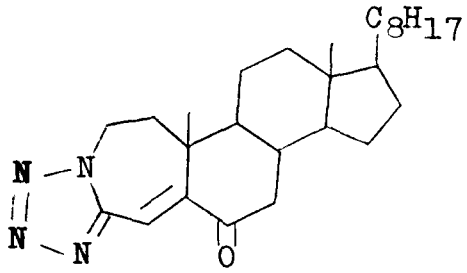
Spectral data of some steroidal tetrazoles

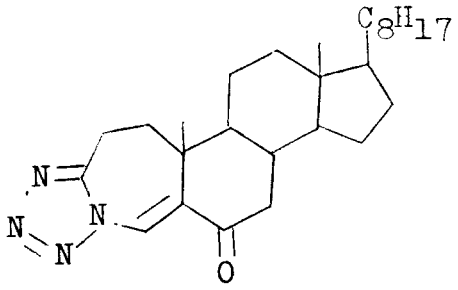
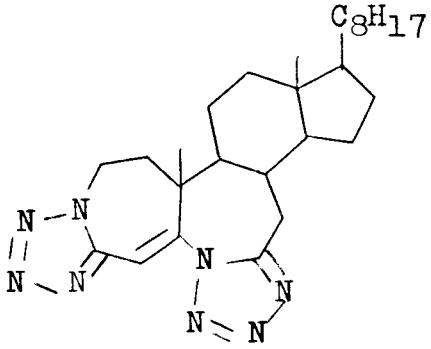
Compound	UV $\lambda_{max.}$ (nm)	IR $\nu_{max.}$ (cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XXXII)	272(log ε 4.42)	1650 (C=C); 1500 (C=N); 1465, 1380 (N=N)	7.53, s(C6-H); 4.45,br(C8-H); 2.5, m(C3-H_2); 1.23,s(C10-CH_3); 0.76,s(C13-CH_3); 0.96 and 0.85(remaining methyl protons)	32
 (XXXIII)		3030 (cyclopropane); 1525 (C=N); 1460, 1365 (N=N)	3.36, d(C7a-H); 0.96, s(C10-CH_3); 0.66, s(C13-CH_3); 0.91 and 0.81(remaining methyl protons)	32

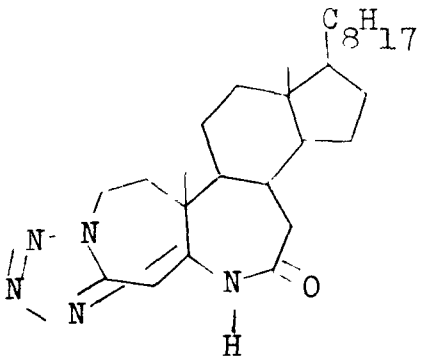
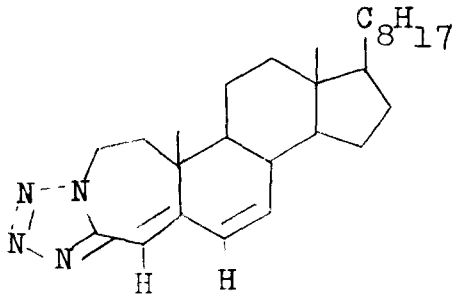
Compound	UV $\lambda_{max.}$ (nm)	IR $\nu_{max.}$ (cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XXXIV)	240(log ε 4.13)	1660 (C=C); 1505 (C=N); 1470, 1380(N=N)	6.63, s(C6-H); 4.21, br(N-C8-H); 3.81, br(C3-αH ; $W_{\frac{1}{2}}$ = 22Hz); 1.38, s(C10-CH_3); 0.80, s(C13-CH_3); 1.0, 0.92 and 0.83 (remaining methyl protons).	32
 (XXXV)		3400 br(OH); 1540 (C=N); 1480,1390(N=N)	4.33, dd(C5-H ; J = 12 and 7 Hz); 3.75, br(C3α-H); 3.38, d(C7a-H; J = 15 Hz); 0.52, s(C13-CH_3); 0.91, 0.81 and 0.63 (remaining methyl protons).	33

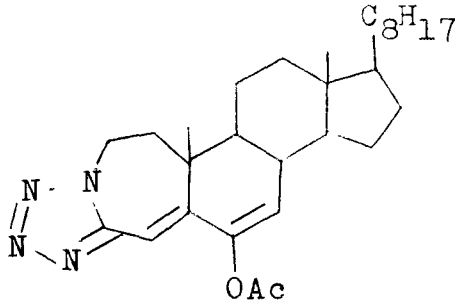
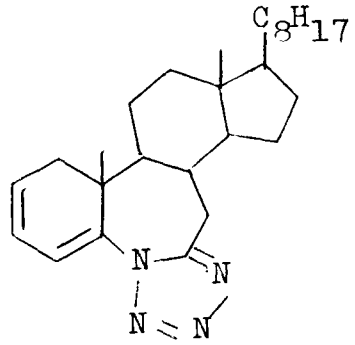
Compound	UV $\lambda_{max.}$ (nm)	IR $\nu_{max.}$ (cm^{-1})	^{1}H-NMR δ (ppm)	Ref.
 (XXXVI)		3340, 3200 (NH); 1690, 1640 (CONH); 1540 (C=N); 1470, 1380 (N=N)	7.0, br(N<u>H</u>; exchangeable with D_2O); 4.66, br(C5-<u>H</u>); 4.06, m(C4a-<u>H_2</u>); 3.41, m(C7a-<u>H_2</u>); 0.45, s(C13-C<u>H_3</u>); 0.91, 0.81 and 0.65 (remaining methyl protons).	33
 (XXXVII)		1722 (C=O); 1530 (C=N); 1460, 1360 (N=N)	4.66, dd(C5-H; J = 13 and 6 Hz); 3.5, m(C7a-<u>H</u>); 0.68, s(C13-C<u>H_3</u>); 0.91, 0.81 and 0.73 (remaining methyl protons).	33

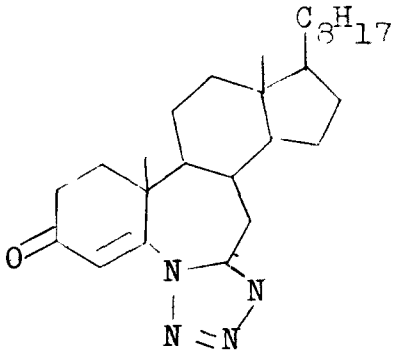
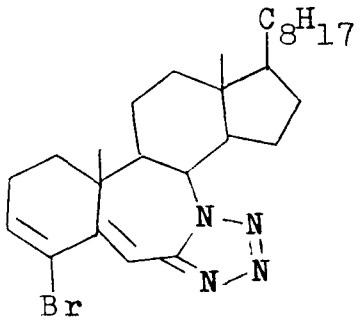
Compound	UV λ max.(nm)	IR ν max.(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XXXVIII)		1540 (C=N); 1460, 1380(N=N)	4.26, dd (C5-αH; J = 10 and 7Hz); 3.21, d(C7a-H; J = 15Hz); 0.43, s(C13-CH_3); 0.90, 0.81 and 0.63 (remaining methyl protons)	33
 (XXXIX)		1540 (C=N); 1470, 1390(N=N)	5.58. dist. d (C5-αH. J = 10Hz and 6Hz); 5.00, dd(C4a-H; J = 10Hz); 3.55, d(C7a-H; J = 15Hz) and 3.13, m($C2-H_2$)	34

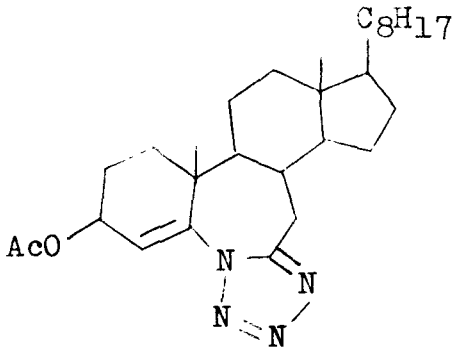
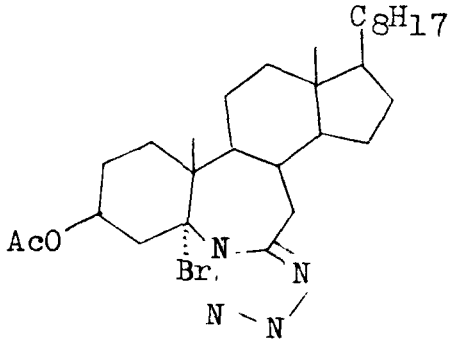
Compound	UV $\lambda_{max.}$(nm)	IR $\nu_{max.}$(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XL)		3400-3200 br(OH); 1715 (C=O); 1545 (C=N); 1480, 1390 (N=N)	5.05,d(C4a-H); 4.41,d(C4a-H; J = 16 Hz and AB System centered at 4.73); 3.25, m(C2-H_2); 0.90 and 0.80 (remaining methyl protons).	34
 (XLI)	260 (log ε 4.38)	1690 (C=C-C=O); 1625 (C=C); 1520 (C=N); 1460, 1380 (N=N)	7.13, s(C4a-H); 4.56, m(C2-H_2); 1.11, s(C10-CH_3); 0.75, s(C13-CH_3); 0.91 and 0.81 (remaining methyl protons).	34

Compound	UV $\lambda_{max.}$(nm)	IR $\nu_{max.}$(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XLII)	243 (log ε 4.1)	1690 (C=C-C=O); 1620 (C=C); 1520 (C=N); 1455, 1380 (N=N)	7.8, s(C4a-H); 3.26, m(C2-H_2); 1.13, s(C10-CH_3); 0.73, s(C13-CH_3); 0.90 and 0.81 (remaining methyl protons).	34
 (XLIII)	245 (log ε 4.4)	1670 (C=C); 1530 (C=N); 1460, 1375 (N=N)	7.03, s(C4a-H); 4.68, m(C2-H_2); 3.45, d(C7a-H; J = 15 Hz); 0.91 0.81 and 0.73 (remaining methyl protons).	34

Compound	UV $\lambda_{max.}$ (nm)	IR $\nu_{max.}$ (cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XLIV)	243 (log ε 4.1)	3220 (NH); 1675, 1655 (CONH); 1640 (C=C); 1530 (C=N); 1455, 1350 (N=N)	8.56, s(CONH, exchangeable with D_2O); 6.80, s(C4a-H); 4.58, m(C2-H_2); 1.58, s(C10-CH_3); 0.71, s(C13-CH_3); 0.90 and 0.81 (remaining methyl protons).	34
 (XLV)	287 (log ε 4.41)	1650 (C=C); 1537 (C=N); 1475, 1390 (N=N)	6.36, s(C4a- H); 6.03, m(C6-H and C7-H); 4.51, m(C2-H_2); 1.08, s(C10-CH_3); 0.75, s(C13-CH_3); 0.90 and 0.81 (remaining methyl protons).	34

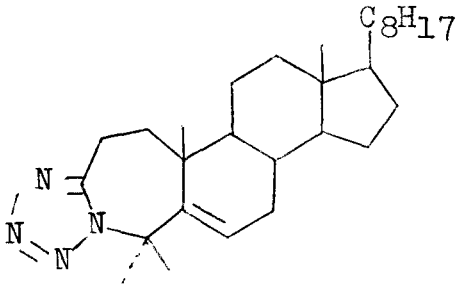
Compound	UV $\lambda_{max.}$(nm)	IR $\nu_{max.}$(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XLVI)	293 (ε 17200)	1760 (CH_3COO); 1625 (C=C); 1520 (C=N); 1465, 1370 (N=N); 1200 (C-O)	6.5, s(C4a-H); 5.56, br(C7-H); 4.46, m(C2-H_2); 2.25, s(CH_3COO); 0.9, s(C10-CH_3); 0.76, s (C13-CH_3).	35
 (XLVII)	280 (ε 10200)	1650 (C=C-C=C); 1590 (C=C); 1510 (C=N); 1460, 1375 (N=N)	6.05, m(C3-H, C4-H); 3.24, d(C7a-H; J = 15 Hz); 0.9, s(C10-CH_3); 0.7, s(C13-CH_3).	35

Compound	UV $\lambda_{max.}$(nm)	IR $\nu_{max.}$(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (XLVIII)	239 (ε 12800)	1690 (C=O); 1640 (C=C); 1515 (C=N); 1465, 1380 (N=N)	6.16, s(C4-H); 3.48, d(C7a-H; J - 15 Hz); 0.9, s(C10-CH_3); 0.7, s(C13-CH_3).	35
 (XLIX)	282 (ε 16700)	1620 (C=C); 1500 (C=N); 1460, 1370 (N=N); 690 (C-Br)	7.2, s(C6-H); 6.46, dist. t (C3-H; J = 5 Hz); 4.52, m(C8-H); 0.93, s(C10-CH_3); 0.80, s(C13-CH_3).	35

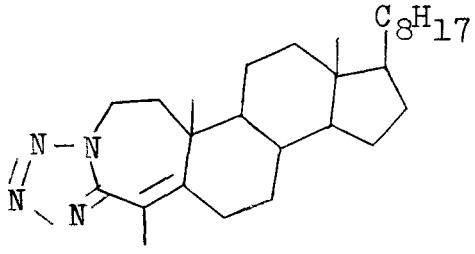
Compound	UV $\lambda_{max.}$(nm)	IR $\nu_{max.}$(cm^{-1})	^{1}H-NMR δ(ppm)	Ref.
 (L)		1730 (CH_3COO); 1642 (C=C); 1510 (C=N) 1460, 1370(N=N); 1230, 1210(CO)	6.1, d(C4-H; J=3Hz); 5.38, br(C3-αH; $W_{\frac{1}{2}}$ = 12 Hz); 3.4, br,d(C7a-H, J=15Hz); 2.11, s(CH_3COO); 0.9, s(C10-CH_3); 0.7, s(C13-CH_3); 0.8 and 0.75 (remaining methyl protons).	36
 (LI)		1725 (CH_3COO); 1520 (C=N); 1435, 1360 (N=N)	5.3, br(C3-αH; $W_{\frac{1}{2}}$ = 16 Hz); 3.4, d(C7a-H; J=15Hz); 2.03,s(CH_3COO); 0.93,s(C10-CH_3); 0.66,s(C13-CH_3); 0.83 and 0.76(remaining methyl protons).	36

Discussion

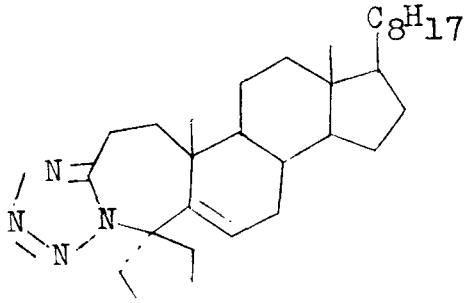
Interest in the field of steroidal tetrazoles have been created because of the biological activities associated with them and their uses as potential drugs. As a result of this realization more importance was given towards the syntheses of steroidal tetrazoles. Numerous papers appeared describing the preparation of tetrazoles from various steroidal ketones. Previous work from this laboratory described the preparation of 4-aza-A-homo-4a,4a-dimethylcholest-5-eno[4,3-d]tetrazole (LII) 3-aza-A-homo-4a-methylcholest-4a-eno[3,4-d]tetrazole(LIII), 4-aza-A-homo-4a,4a-diethylcholest-5-eno[4,3-d]tetrazole (LIV) and 4-aza-A-homo-4a-ethylcholest-4a-eno[4,3-d]tetrazole (LV)[37].



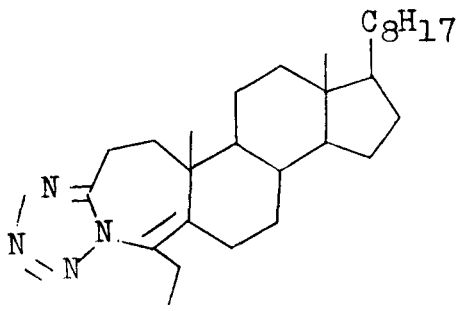
(LII)



(LIII)

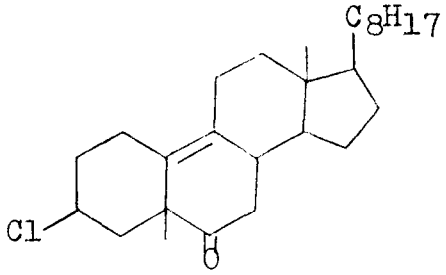


(LIV)

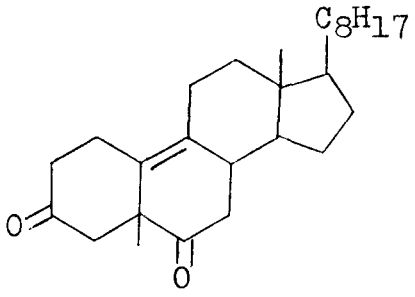


(LV)

The present work describes the preparation of tetrazoles derived from steroidal ketones such as 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI) and 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (LVII).



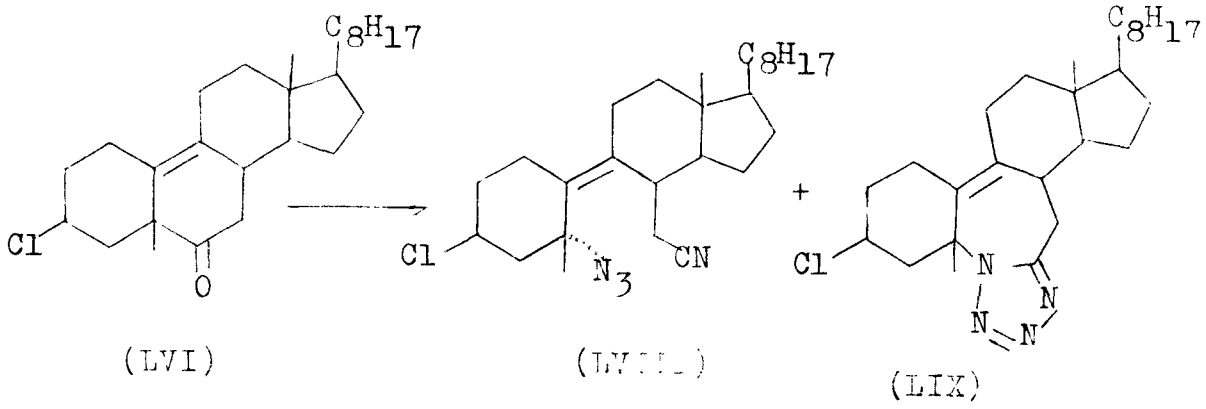
(LVI)



(LVII)

Reaction of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI) with an excess of hydrazoic acid-BF_3-etherate

3β-Chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI)[38] was treated with an excess of hydrazoic acid (prepared according to the method described by Moural and Syhora)[39] in the presence of BF_3-etherate. After work up and column chromatography over silica gel two products, a non-crystallizable oil and a solid m.p. 151° were separated.



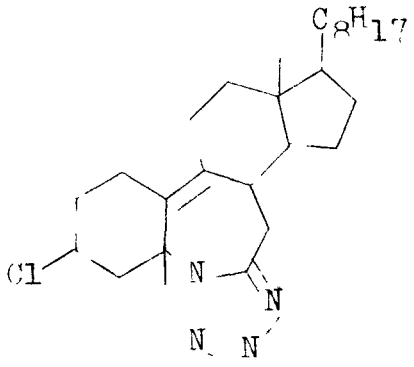
Characterization of the oily compound as 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (LVIII)

The oily compound analysed for $C_{27}H_{43}N_4Cl$. The presence of chlorine was assured by positive Beilstein test. In the IR spectrum bands at 2245 and 2100 cm^{-1} indicated the presence of nitrile and azide functions respectively which often results, as product of reaction with a ketone adjacent to a tetra substituted carbon. Its NMR spectrum gave a broad multiplet centered

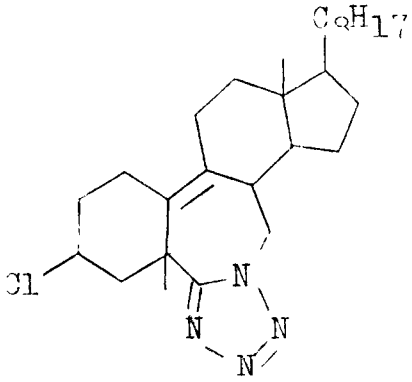
at δ 4.2 integrating for one proton with half band width of 16 Hz, ascribable to C3-α$\underline{H}$ (axial)[40]. There was no signal for C7a-methylene protons because they have been merged with methylene envelop, a similar observation as reported[33] earlier. A sharp singlet at δ 1.65 integrating for 3 protons can be assigned to C5-β methyl protons. Angular and other methyl protons appeared at δ 0.68 (C13-C$\underline{H}_3$), 0.9 and 0.81 (other methyl protons). On the basis of the above discussion oily compound may be characterized as 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (LVIII).

Characterisation of the compound, m.p. 151° as 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole(LIX)

The compound, m.p. 151° was analysed for $C_{27}H_{43}N_4Cl$ (positive Beilstein test), indicating the addition of four nitrogen atoms to the parent compound (LVI). Its IR spectrum exhibited bands at 1500, 1455 and 1370 cm^{-1} (C=N, N=N) for tetrazole ring. A band at 760 cm^{-1} (C-Cl) can be assigned to axially oriented chlorine[41] at C3. On the basis of this data two isomeric structures can be written for the compound, m.p. 151° i.e. 6-aza-B-homo-[6,7-d]tetrazole (LIX) or the alternate 7-aza-B-homo-[7,6-d] tetrazole (LX). A clear distinction between the two was made possible with the help of NMR spectrum of this compound.

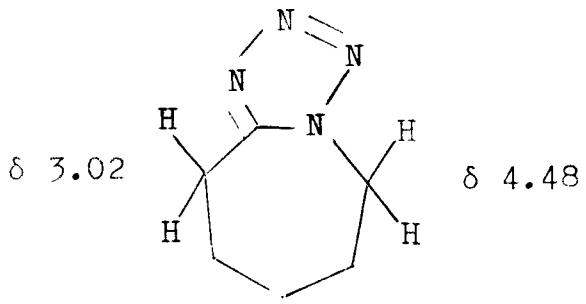


(LIX)



(LX)

It has been reported by Di Maio and Permutti[42] that NMR spectrum of the tetrazole (LXI) exhibits a two protons multiplet at δ 4.48 which is ascribable to the methylene group directly attached to the ring nitrogen atom and another two protons multiplet as δ 3.02 due to the methylene group adjacent to C=N fragment of the tetrazole moiety.



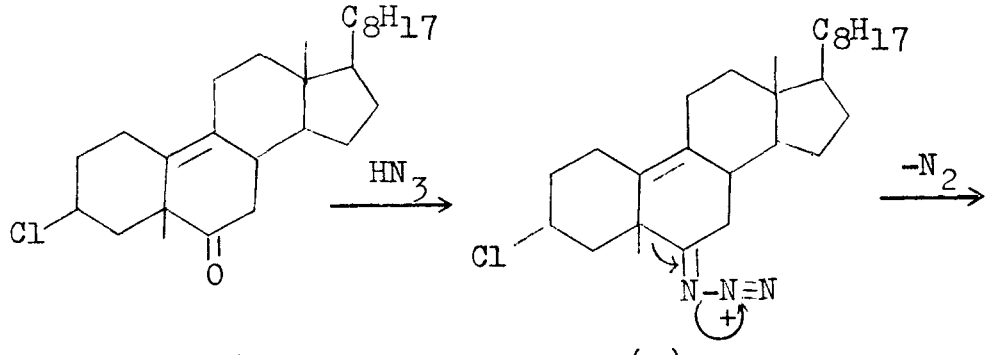
(LXI)

The NMR spectrum of the compound m.p. 151° gave a broad multiplet centered at δ 3.88 (1H, $W_{\frac{1}{2}}$ = 12 Hz, C3-α<u>H</u>, equatorial)[40]. The distinction between the two possible isomeric structures (LIX and LX) was based upon the signal for C7a-proton. There was no signal in the region (δ 4-5) corresponding to protons adjacent to nitrogen as in (LX) which discarded this possibility. Instead there was a signal in the NMR spectrum for one of the C7a-protons at δ 3.45. It has been observed[33] that in tetrazoles obtained from saturated ketones only one of the C7a-protons appeared around δ 3.5 as the other C7a-proton remains uninfluenced by the electron withdrawing nature of tetrazole ring and gets merged with the methylene envelop. Further the C7a-proton which is pseudo axial in nature has got a dihedral angle of about 90° with the axial C8-β<u>H</u>. For this reason there is no vicinal coupling and the C7a-proton (pseudo axial) is geminally coupled with the other C7a-proton to a magnitude of 15Hz. However, in this spectrum C7a-proton (axial like) interestingly does not appear as a clean doublet. It is seen that this doublet which has a J value of 16Hz further splits and the J value between the two parts of each doublet is 6Hz. This difference in splitting seems due to the different ring juction (cis) and the presence of C9-C10 double bond in (LIX). Interestingly the signal for C13-methyl protons resonates at normal position (δ 0.65) in comparison to (XXXV) which showed a remarkable diamagnetic shift. It appears that the introduction of C9-C10 double bond and ring junction (cis) in LIX alters the position of C13-methyl protons.

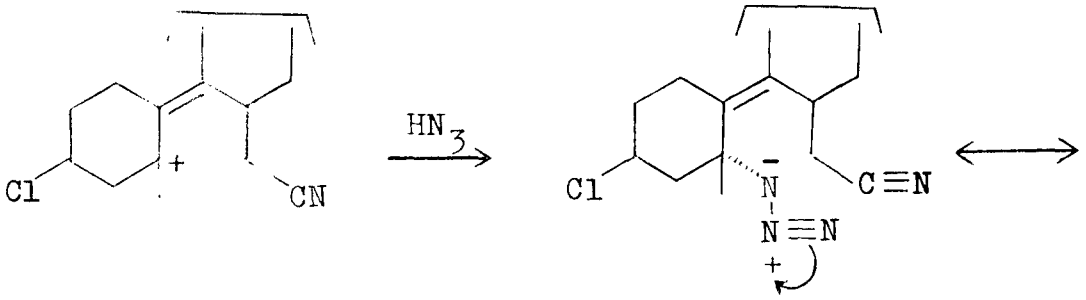
The C5-β methyl signal was observed at δ 1.81 and other methyl signals were observed at δ 0.88, 0.75 and 0.65 (C13-C$\underline{H}_3$). On the basis of the foregoing discussion compound, m.p. 151° is regarded as 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (LIX).

The intermediacy of (LVIII) during the course of formation of LIX from LVI was experimentally substantiated, when the oil (LVIII) was heated for 15 mts, under went cyclization to the chloro tetrazole (LIX). M.p., m.m.p. and spectral values of this cyclized tetrazole were comparable to the one directly isolated. This observation is analogous to the previously recorded one in literature[25,26].

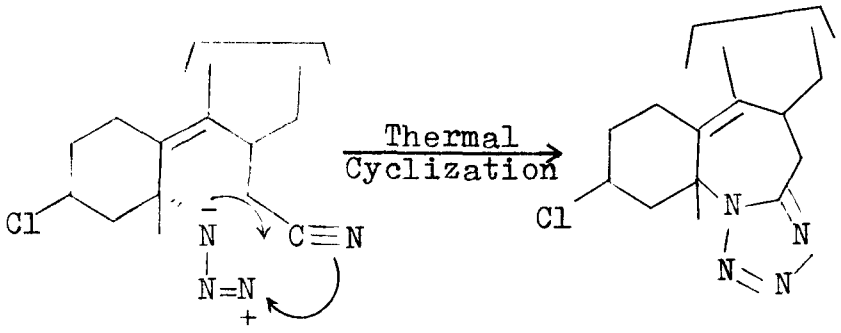
This novel cleavage of 6-oxosteroid to azido nitrile and its subsequent cyclization to tetrazole, finds analogy with the mechanism through which 17-oxo-steroids are shown to undergo cleavage to azido nitrile and then thermally cyclized to tetrazoles[25,26] Following reaction sequence depicts the stages through which 6-oxo-steroid (LVI) is converted to tetrazole (LIX).



(LVI) (a)



(b) (c)

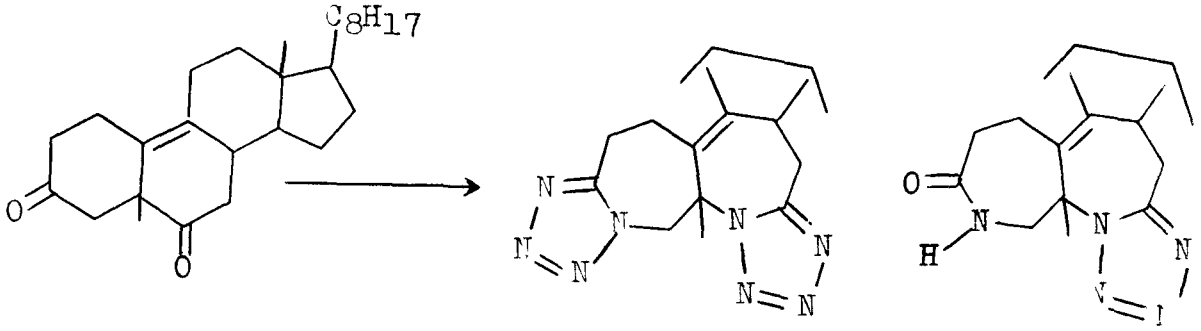


(LVIII) (LIX)

The mechanism satisfactorily accounts for the observed stereospecificity, the carbonium ion (b) retaining its configuration and instantly reacting with hydrazoic acid to (c). However, the possibility of concerted reaction involving the approach of azide ion from the rear in (a) leading to (c) can not be excluded. Since, for intermolecular reaction without a catalyst it seems particularly necessary that the nitrile function be sufficiently activated by electron withdrawing group[43]; this kind of reaction may be termed as 1,3-dipolar addition.

Reaction of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (LVII) with an excess of hydrazoic acid - BF_3-etherate

The diketone (LVII)[44] on reaction with an excess of hydrazoic acid followed by usual workup of the reaction mixture and column chromatography over silica gel provided two compounds, m.p. 120° (major) and 110° (minor).

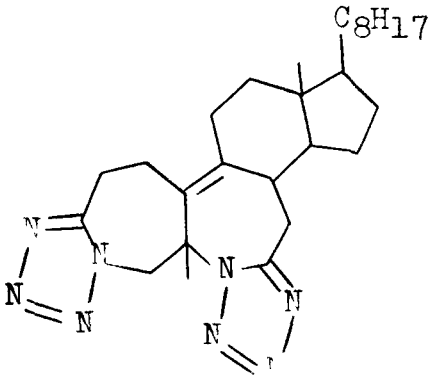


(LVII) (LXII) (LXIII)

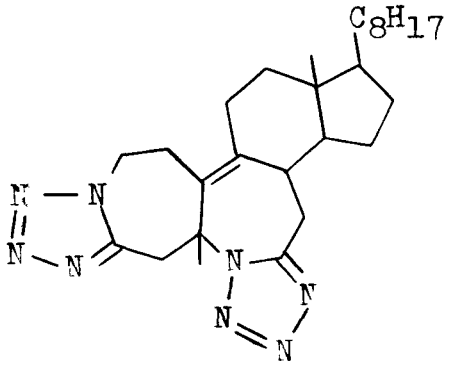
Characterisation of the compound, m.p. 120° as 4,6-diaza-A,5-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[4,3-d], [6,7-d] bistetrazole (LXII)

The compound m.p. 120° was analysed for $C_{27}H_{42}N_8$. Its IR spectrum exhibited bands at 1520 (C=N), 1460 and 1380 cm^{-1} (N=N) (for tetrazole moiety). Bands for carbonyl, nitrile, azide and amide functions were not observed in its IR spectrum. Thus the

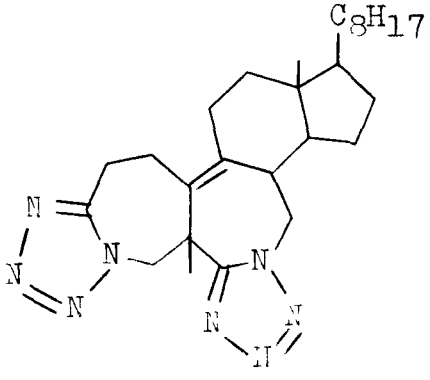
molecular composition and IR values suggested the formation of a bistetrazole. The following four possible structures may be formulated for the compound m.p. 120°. Its NMR spectrum was helpful in arriving at the conclusion that the compound, m.p.120° has the structure (LXII). It gave an unresolved signal at δ 5.52 integrating for two protons which is ascribable to C4a-protons.



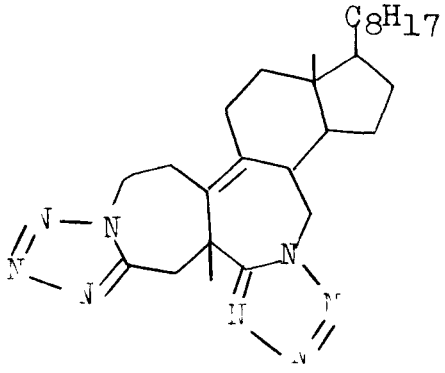
(LXI)



(LXI)



(LX)



(LXVI)

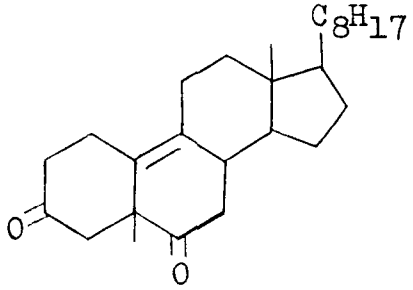
its appearance at, as lower as δ 5.52 is quite justified as it is flanked between two tetrazole rings and therefore experiences a paramagnetic effect[34]. Distorted doublet at δ 3.81 and a multiplet at δ 4.7, both integrating for two protons each can be ascribed to the C7a and C2 methylene protons respectively. The downfield shift of these protons[42] is attributed to the two tetrazole moieties, the cis A/B junction and the C_{9-10} double bond as in structure (LXII). A sharp peak at δ 2.13 integrating for three protons may well be considered for C5-β methyl protons adjacent to 6-aza-B-homo[6,7-d]tetrazole moiety which is responsible for the downfield shift of C5-methyl protons. In the light of the above discussions the compound, m.p. 120° may be characterized as 4,6-diaza-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[4,5-d][6,7-d]bistetrazole (LXII).

Characterization of the compound, m.p. 110° as 4,6-diaza-3-oxo-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (LXIII)

The compound, m.p. 110° was analysed for $C_{27}H_{43}N_5O$. Its IR spectrum exhibited bands at 3150 (NH), 1670 (CONH), 1535 (C=N), 1460 and 1380 cm^{-1} (N=N). These values suggest that the compound is possibly a lactam tetrazole. In its NMR spectrum the NH signal exchangeable with deuterium was observed at δ 7.18 as a broad

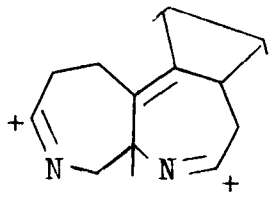
multiplet. In view of the fact that tetrazole and lactam originate from a common precursor it is possible that the compound has also got the 4-aza structure (LXIII) as in structure (LXII). The C4a-methylene protons were observed at δ 5.27 as an unresolved multiplet. Such a downfield shift of the signal is indeed justified because of the neighbouring tetrazole ring which is electron withdrawing. The signal for C7a-protons was obtained as an unresolved multiplet type at δ 3.50. The C5-β methyl signal was found at δ 2.08 and the remaining methyl protons were bunched together at δ 0.91 and 0.83.

The following reaction pathway accounts for the formation of the tetrazole (LXII) and the lactam (LXIII) from the ketone (LVII).

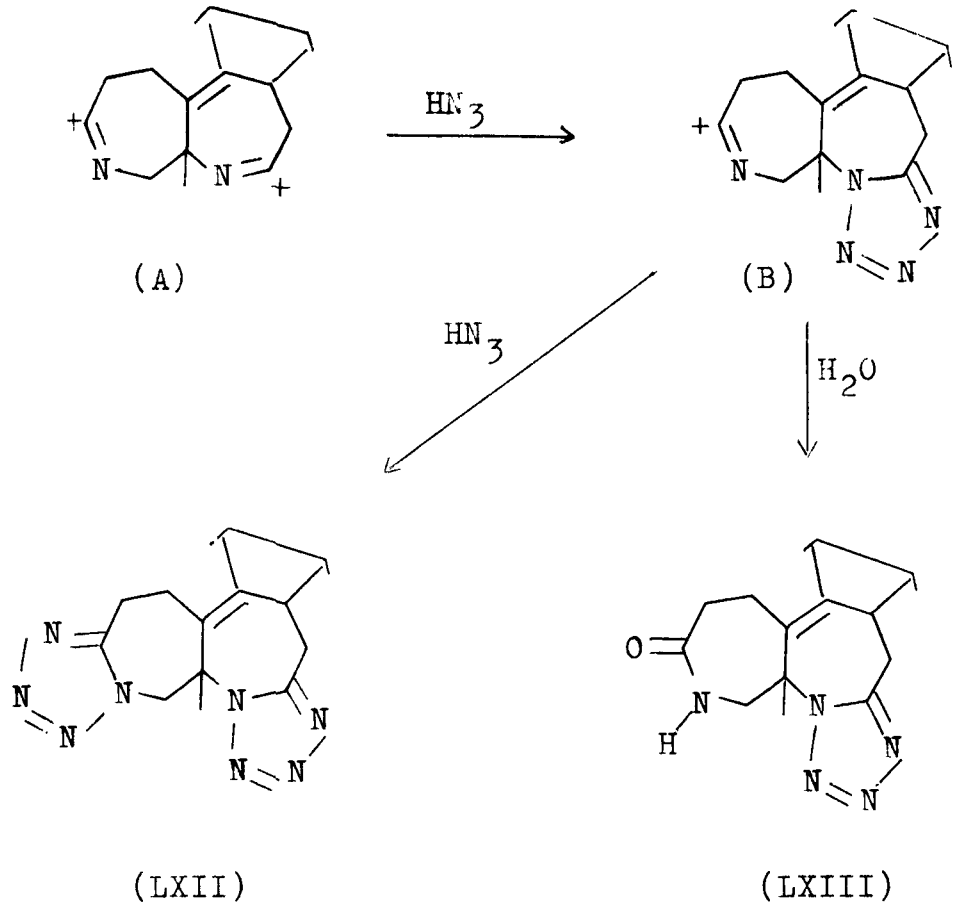


(LVII)

$2HN_3$



(A)



Addition of hydrazoic acid to imidocarbonium ion intermediate (B) leadsto the formation of tetrazole (LXII) where as the addition of water resulted in the formation of lactam (LXIII).

Experimental

All melting points are uncorrected. IR spectra were determined in Nujol with a Perkin-Elmer 237 Spectrophotometer. NMR spectra were run in $CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. TLC plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as the spraying reagent. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate was used as the drying agent. NMR values are given in ppm (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet). IR values are given in cm^{-1}.

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened the mixture was gently heated at a temperature of 50-60° on a water bath for one hour and then poured into crushed ice-water with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cooled water and air dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (95 g), m.p. 95-96° (reported[45] m.p. 96-97°).

3β-Chloro-5,6β-dihydroxy-5α-cholestane

3β-Chlorocholest-5-ene (28 g) in hot acetic acid (500 ml)

was treated with hydrogen peroxide (120 ml, 30%) and kept at 95° for 30 minutes. After removal of the solvent under vacuum the oily product obtained was extracted with ether. Evaporation of the solvent provided an oil (29 g) which was chromatographed on alumina (600 g). Elution with benzene:pentane (3:7) gave unreacted compound (3.36 g). Elution with ether gave (15 g) 3β-chloro-5,6β-dihydroxy-5α-cholestane, which was recrystallized from ether:pentane, m.p. 126° (reported[46] m.p. 126°).

3β-Chloro-6β-acetoxy-5α-hydroxycholestane

3β-Chloro-5,6β-dihyroxy-5α-cholestane (50 g) was dissolved in pyridine (75 ml) and acetic anhydride (50 ml) was added. The mixture was relfuxed on water bath for 2 hours. The resulting solution was poured into crushed ice-water mixture with stirring. A solid was obtained which was filtered under suction, washed with water until free from pyridine and air dried. The crude product on recrystallization from methanol gave 3β-chloro-6β-acetoxy-5α-hydroxycholestane (45 g) m.p. 150° (reported[46] m.p. 150-151°).

3β-Chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6β-yl acetate

A mixture of 3β-chloro-6β-acetoxy-5α-hydroxycholestane (10 g), potassium hydrogen sulphate (40 g) and acetic anhydride (100 ml) was heated on a steam bath for one hour. The resulting solution was poured into cold water and extracted with ether. The solvent when evaporated gave an oil which was dried

in vacuum. A semi solid thus obtained, on recrystallization from light petroleum ether gave 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6β-yl acetate (5 g) m.p. 87-89° (reported[47] m.p. 87-88°).

3β-Chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI)

A mixture of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6β-yl acetate (5 g) and 5% methanolic potassium hydroxide (300 ml) was refluxed on steam bath for 2 hours. The resulting solution was poured into ice-cold water, acidified by adding HCl. The solution was worked up in the usual manner.[38] The solvent was evaporated. The residue obtained was dissolved in acetone (250 ml) and the solution was cooled to 0°. It was stirred for 5 minutes and Jones reagent was gradually added with stirring till brown colour persisted. The mixture was allowed to remain at this temperature for 30 minutes. Water (200 ml) was added and extracted with ether. The solvent when evaporated gave an oil which on crystallization from petroleum ether gave 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI) (2.5 g) m.p.63-64° (reported[38] m.p. 64°).

Analysis Found : C, 77.32; H, 10.24

$C_{27}H_{43}OCl$ requires : C, 77.51; H, 10.28%

IR : $\nu_{max.}$ 1720 (C=O), 745 cm^{-1} (C-Cl)

NMR : δ 4.41 m (C3-α$\underline{H}$), 1.42 (C5-β$C\underline{H}_3$), 0.78 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

Reaction of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI) with hydrazoic acid-BF_3-etherate: 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (LVIII) and 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno [6,7-d]tetrazole (LIX)

To a solution of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (LVI) (2 g) in benzene (25 ml) at 0-5° was added excess of hydrazoic acid and freshly distilled BF_3-etherate (2 ml) over a period of 5 hours. The reaction mixture was left at room temperature for 3 days. After the reaction was complete the reaction mixture was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil (1 g) which was chromatographed over a column of silica gel (20 g). Elution with light petroleum ether:ether (19:1) provided an oily product (LVIII), (150 mg).

Analysis Found : C, 70.64; H, 10.11; N, 12.34

$C_{27}H_{43}N_4Cl$ requires : C, 70.74; H, 9.38; N, 12.22%

IR : $\nu_{max.}$ 2245 (CN), 2100 ($-N_3$), 760 cm^{-1} (C-Cl)

NMR: δ 4.2 (C3-α$\underline{H}$), 1.65 (C5-β$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.9 and 0.81 (remaining methyl protons).

Further elution with chloroform yielded a solid compound (LIX) which was recrystallized from ethyl alcohol (100 mg), m.p. 151°.

Analysis Found : C, 70.53; H, 9.41; N, 12.32

$C_{27}H_{43}N_4Cl$ requires : C, 70.74; H, 9.38; N, 12.22%

IR : $\nu_{max.}$ 1500 (C=N), 1455, 1370 (N=N), 760 cm^{-1} (C-Cl)

NMR: δ 3.88 (C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 12Hz), 3.45 (C7a-$\underline{H}$), 1.81 (C5-β$C\underline{H}_3$), 0.65 (C13-$C\underline{H}_3$), 0.88 and 0.75 (remaining methyl protons).

Thermal cyclisation of (LVIII) to (LIX)

3β-Chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile(LVIII)(100 mg) was heated at 225° for 15 minutes. A solid obtained was recrystallized from ethyl alcohol (60 mg) m.p. 151°. It was found identical with 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (LIX) in all respects.

3β,5,6β-Trihydroxy-5α-cholestane

A mixture of cholesterol (20 g) and formic acid (28 ml; 88%) was heated on a water bath at 70-80° for 5 minutes and then allowed to attain room temperature. Hydrogen peroxide (20 ml; 30%) was added to the mixture and it was kept at room temperature for 12 hours with occasional shaking. Boiling water (300 ml) was added with stirring and the reaction mixture was allowed to attain room temperature. A white granular solid thus separated was filtered under suction and air dried. The solid was dissolved in methanol (600 ml) and the solution was heated with sodium hydroxide solution (20 ml; 25%) for 10 minutes, on a steam bath.

It was acidified with hydrochloric acid and diluted with boiling water (700 ml). A solid obtained on cooling was collected by filteration under pressure and air dried. Recrystallization from methanol gave 3β,5,6β-trihydroxy-5α-cholestane (18 g), m.p. 237-239° (reported[48] m.p. 237-239°).

5-Hydroxy-3β,6β-diacetoxy-5α-cholestane

3β,5,6β-Trihydroxy-5α-cholestane (50 g) was dissolved in pyridine (150 ml). Acetic anhydride (100 ml) was added and the reaction mixture was heated on a water bath for 3 hours. The resulting solution was poured on to crushed ice-water mixture with stirring. A solid obtained was filtered under suction washed with water (until free from pyridine) and air dried. The crude product was recrystallized from methanol to give 5-hydroxy-3β,6β-diacetoxy-5α-cholestane (45 g), m.p. 165-166° (reported[44] m.p. 166°).

3β,6β-Diacetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene

A mixture of 5-hydroxy-3β,6β-diacetoxy-5α-cholestane (10 g), potassium hydrogen sulphate (40 g) and acetic anhydride (300 ml) was heated on a steam bath for 2 hours. The resulting solution was poured into water. A solid obtained was filtered under suction, washed with water and air dried. The crude product thus obtained was recrystallized from aqueous acetone to afford 3β,6β-diacetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene (4.5 g

m.p. 127-128°(reported[44] m.p. 128°).

3β,6β-Dihydroxy-19-nor-5-methyl-5β-cholest-9(10)-ene

A mixture of 3β,6β-diacetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene (4 g) and 5% methanolic potassium hydroxide (300 ml) was refluxed on a water bath for 2 hours. The resulting solution was poured into ice-cold water. The reaction mixture was acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with water, sodium hydrogen carbonate solution (5%), water and dried over anhydrous sodium sulphate. Evaporation of the solvent provided a residue, which was recrystallized from methanol to give 3β,6β-dihydroxy-19-nor-5-methyl-5β-cholest-9(10)-ene (3.5 g) m.p.84-86° (reported[44] m.p. 82-87°).

5-Methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (LVII)

3β,6β-Dihydroxy-19-nor-5-methyl-5β-cholest-9(10)-ene (4 g) was dissolved in acetone (250 ml) and the solution was cooled at 0-5°. The solution was stirred for 5 minutes and Jones reagent was gradually added with stirring till a brown colour persisted. The mixture was allowed to remain at this temperature for 30 minutes. Water (200 ml) was added and extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate (anhydrous). The solvent was evaporated to yield an oil. Crystallization from acetone-methanol gave 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (LVII) (2.0 g) m.p. 102-104° (reported[44] m.p. 105-106°).

Reaction of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione(LVII) with hydrazoic acid-BF_3-etherate:4,6-diaza-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[4,3-d][6,7-d]bistetrazole (LXII) and 4,6-diaza-3-oxo-A,B-bishomo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (LXIII)

A solution of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (LVII)[44] (2 g) in benzene was treated with an excess of hydrazoic acid-BF_3-etherate as in the previous case. After the completion of the reaction, the reaction mixture was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. The residue obtained on evaporation of the solvent was chromatographed over a column of silica gel. Elution with benzene:ether (2:1) provided a solid which when recrystallized from petroleum ether gave the compound (LXII) (500 mg) m.p. 120°.

Analysis Found : C, 67.75; H, 8.53; N, 23.91

$C_{27}H_{42}N_8$ requires : C, 67.78; H, 8.78; N, 23.43%

IR : $\nu_{max.}$ 1520 (C=N), 1460 and 1380 cm^{-1} (N=N)

NMR : δ 5.52 (C4a-$\underline{H}_2$), 4.7 m(C2-$\underline{H}_2$), 3.81 dist. d(C7a-$\underline{H}$), 2.13 (C5-β$C\underline{H}_3$), 0.75 (C13-$C\underline{H}_3$), 0.95 and 0.85 (remaining methyl protons).

Further elution with benzene:ether (1:1) yielded an oil, crystallized from ethyl alcohol to provide the compound (LXIII) (60 mg) m.p. 110°.

Analysis Found : C, 71.22; H, 9.50; N, 16.1

$C_{27}H_{43}N_5O$ requires : C, 71.52; H, 9.49; N, 15.45%

IR : $\nu_{max.}$ 3150 (NH), 1670 (CONH), 1535 (C=N), 1460 and 1380 cm^{-1} (N=N)

NMR: δ 7.18 (NH), 5.27 (C4a-$\underline{H}_2$), 3.50 (C7a-$\underline{H}$), 2.08 (C5-$\beta C\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons).

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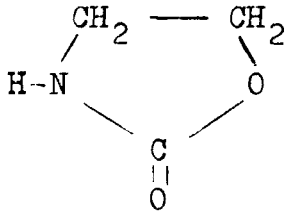
Part Two

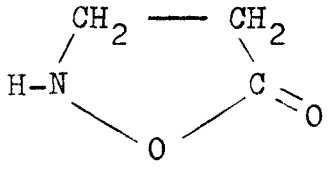
Steroidal Oxazolidinones

Theoretical

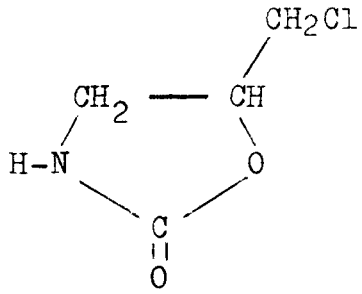
Oxazolidinones (Ia) also referred as oxazolidones are an important class of heterocyclic compounds containing a saturated five membered ring having nonadjacent oxygen and nitrogen atoms joined by a carbonyl group. Its counter part isoxazolidinones (Ib) are with oxygen and nitrogen atoms at adjacent positions. The earliest known 5-chloromethyl-2-oxazolidinone (II) reported by Thomsen[1] was synthesized from epichlorohydrin and potassium cyanate. In a concise review Cornforth[2] has compiled the methods of synthesizing oxazolidinones. The syntheses, reactions and the applications of oxazolidinones were detailed in large by Martin et al.[3] In the recent past much importance was attached to the syntheses of oxazolidinones and its derivatives because of their immense biological activities and industrial usage. Many papers were published covering the syntheses of a number of oxazolidinones.



(Ia)

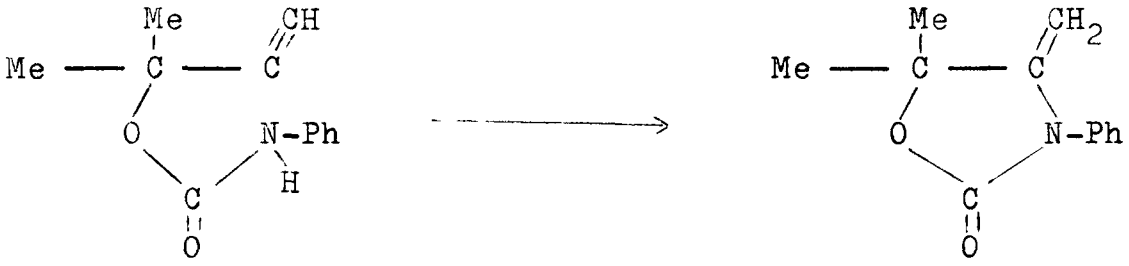


(Ib)

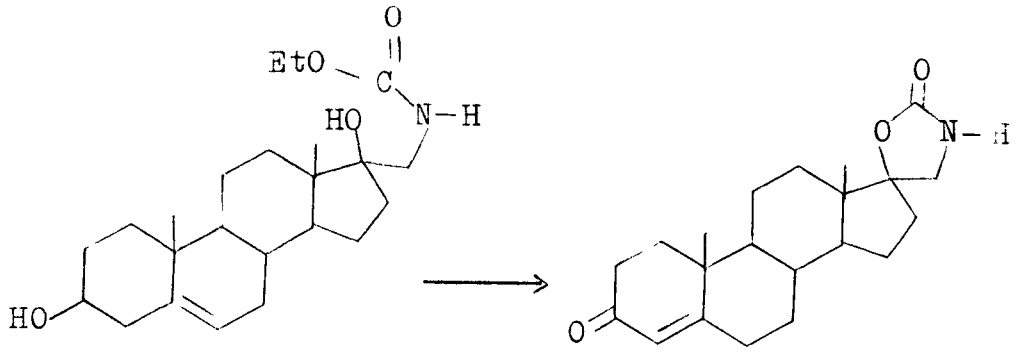


II

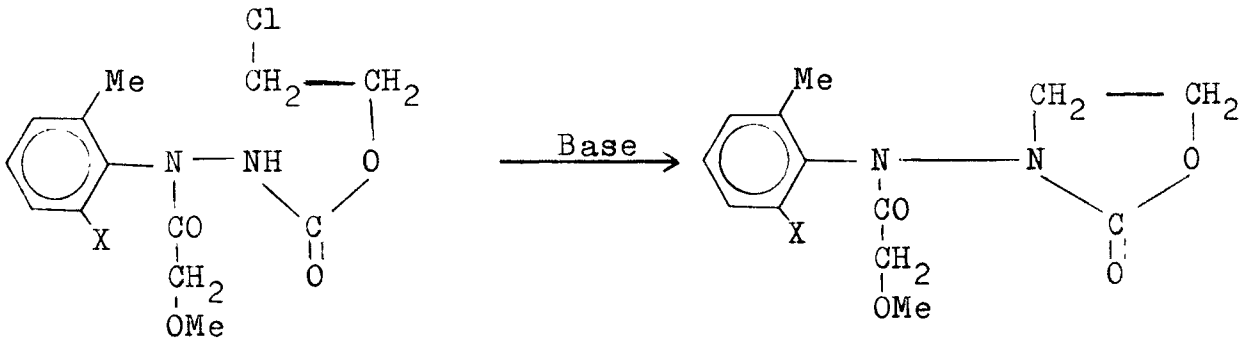
The syntheses generally involved the cyclization of compounds containing the two heteroatoms and a carbonyl group or as in other cases coupling of two or three different molecules containing the heteroatoms. Dovlatyan et al.[4] reported the formation of oxazolidinone (III) by the cyclization of $PhNHCO_2CMe_2C{\equiv}CH$. Similar findings were reported by Francis et al.[5]. Steroidal oxazolidinone (V) was also reported[6] by the cyclization of carbamate (IV). Base was employed[7,8] in the cyclization to prepare the fungicidal oxazolidinones (VIII and IX) from VI and VII.



(III)

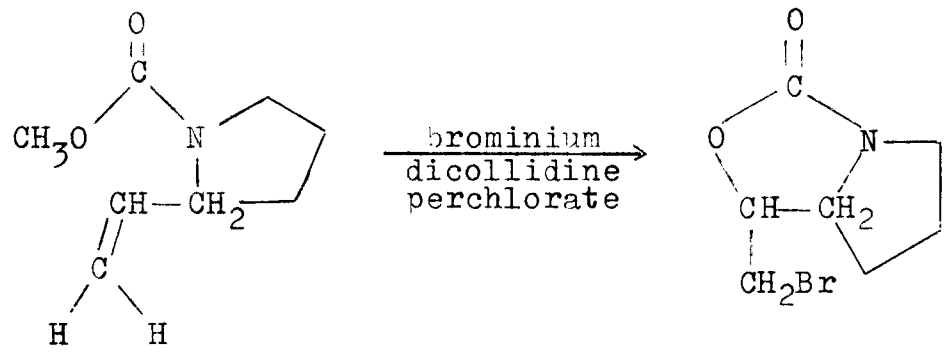


(IV) (V)

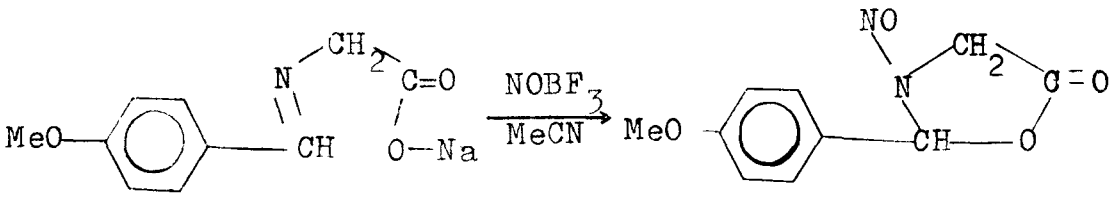


X		X	
(VI)	-Cl	(VIII)	-Cl
(VII)	-Me	(IX)	-Me

Carbamates containing C=C[9-12] (X) or C=N (XII)[13] functions cyclized in the presence of HCl/Br_2 or Br^+ to give oxazolidinones (XI and XIII[13]). Intramolecular cyclization of glycidylphenylurethane at 135° in the presence of Bu_3N was reported[14] to give oxazolidinone.

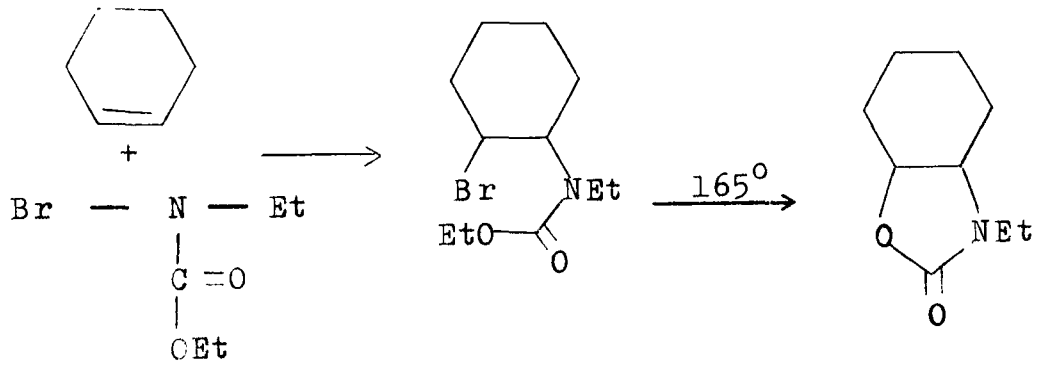


(X) (XI)



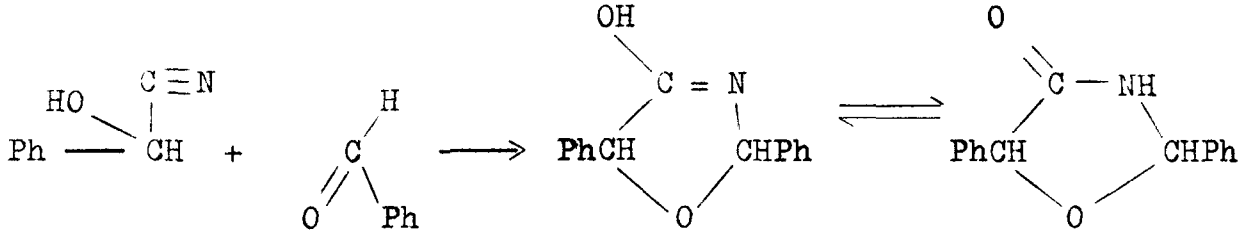
(XII) (XIII)

Halohydrins when treated with isocyanates gave carbamates which were cyclized in the presence of a base to yield[15-17] oxazolidinone. Ethylenic compounds were reported[18-20] to get coupled with short chain N-halo carbamates and then cyclized on heating to give oxazolidinone derivatives (XIV)



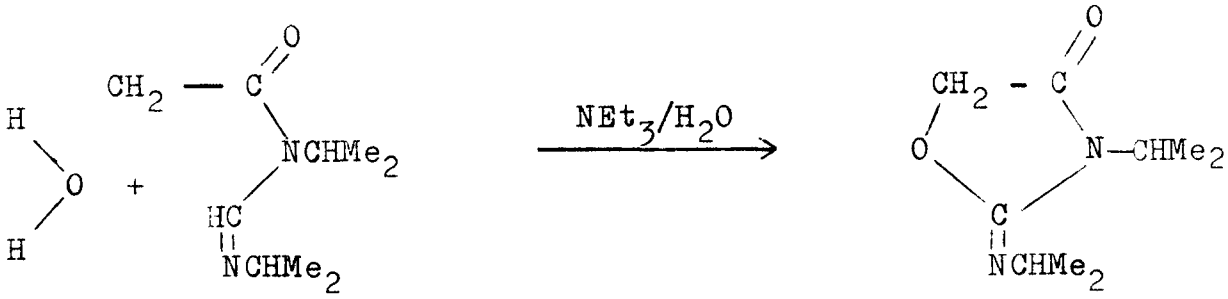
(XIV)

The C=O group of aldehydes was involved[21] in coupling the two ends of carbamates in the formation of oxazolidinones. Condensation of PhCH(OH)CN with PhCHO in Et_2O containing dry HCl at 40° was also reported[22] to give oxazolidinone (XV).



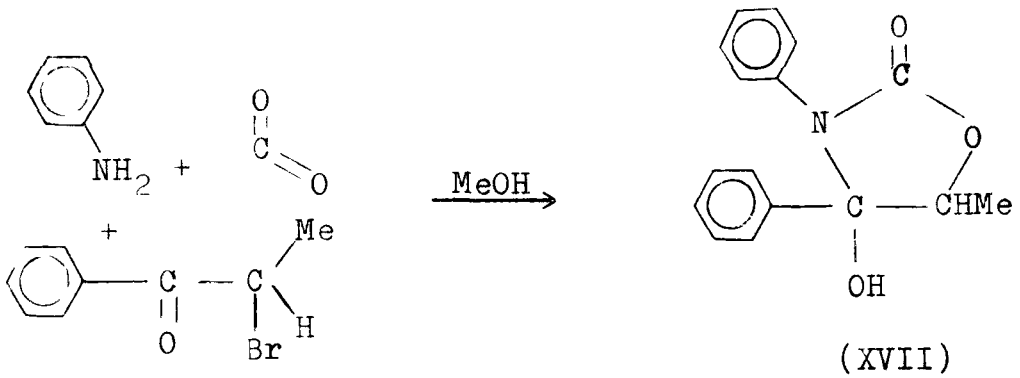
(XV)

Amides and amido alcohols form one of the important class of compounds in the syntheses of oxazolidinones. Cyclization of amidoalcohols with α-chloro substituted ether in the presence of Zn[23] or with an aldehyde in the presence of an acid[24-26] afforded oxazolidinones. Either one[27] or two[28] molecules of amides underwent ring closure in the presence of a base to yield oxazolidinone (XVI)[27].



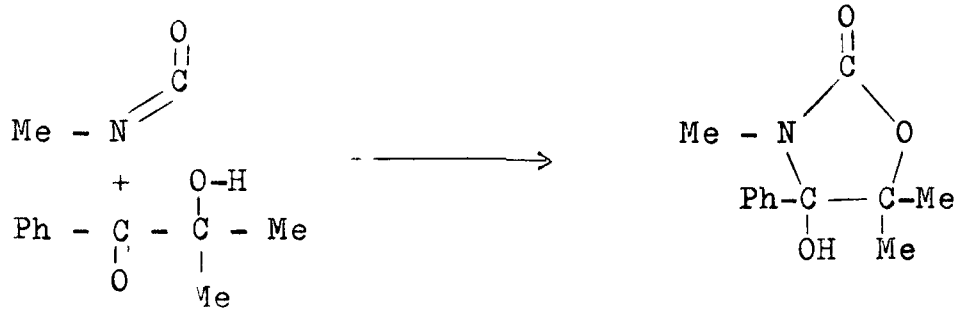
(XVI)

Cyclization of amine with CO_2 leading to the formation of oxazolidinone was reported by Akazaki et al.[29] α-Bromopropiophenone reacted with CO_2 in the presence of an amine to yield oxazolidinone (XVII)[30].

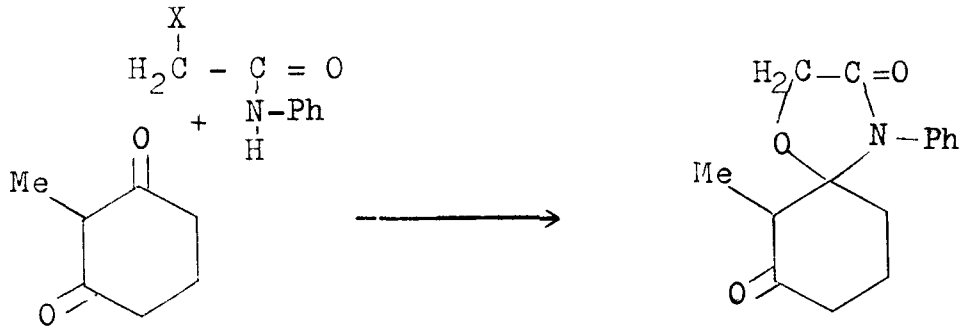


(XVII)

N-Methyl-5,5-dimethyl-4-hydroxy-4-phenyloxazolidin-2-one (XVIII) a useful psychotropic agent was formed[31] by the reaction of α-hydroxybutyrophenone with isocyanate. Spiro-oxazolidinone (XIX) was considered to arise[32] by a reaction of 2-methylcyclohexa-1,3-dione with α-halogenoacetanilide.

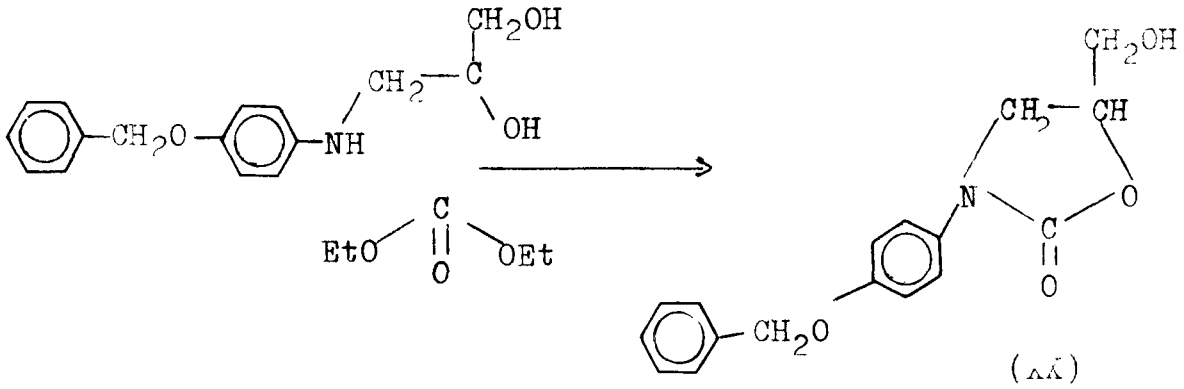


(XVIII)



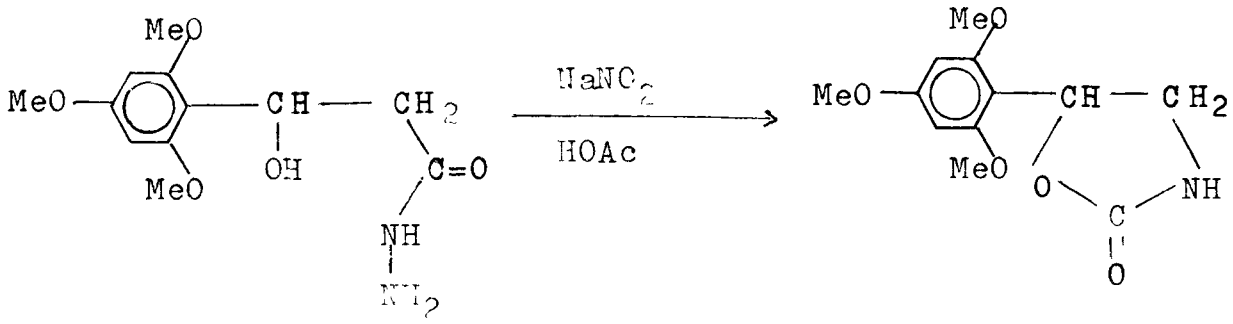
(XIX)

Cyclization of amino alcohol leading to the formation of 2-oxazolidinone (XX) was also carried out with ethylcarbonate[33]. Similar findings were reported by Brawn[34] and $COCl_2$ was also found utilized in the cyclization of amino alcohols[35].

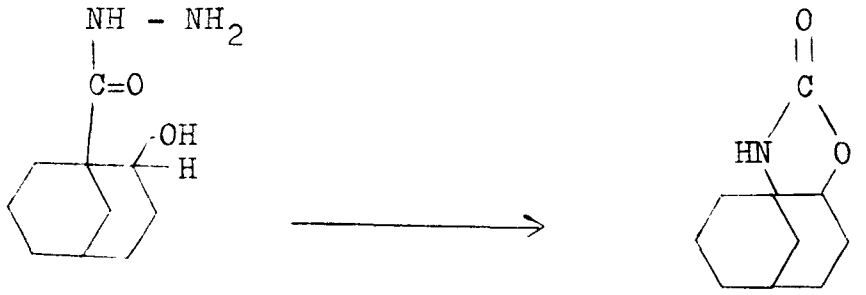


(XX)

The findings of Jaiswal et al.[36] were interesting, that hydrazide (XXI) on treatment with HNO_2, underwent rearrangement followed by ring closure to give oxazolidinone (XXII). Similar products were reported by Zhelyazkov et al.[37,38]. A bicyclo derivative (XXIV) was obtained[39] by the cyclization of hydrazide (XXIII).

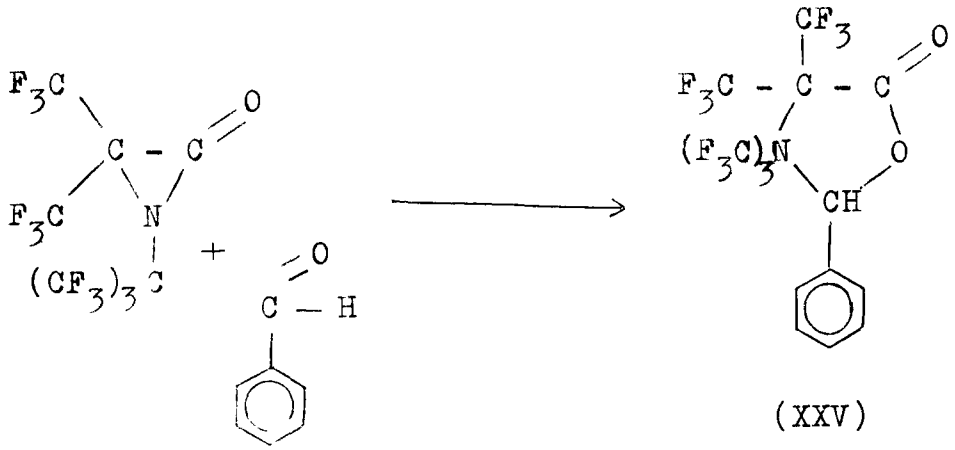


(XXI) (XXII)



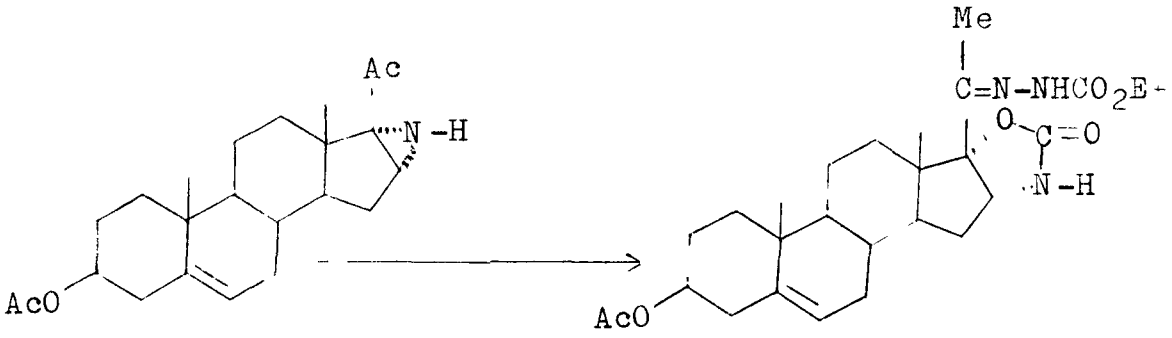
(XXIII) (XXIV)

Acid catalysed aziridine ring opening in the presence of Na_2CO_3[40,41] or CO_2[42,43] lead to the formation of oxazolidinones. Ring enlargement of perfluoro-α-lactam by aldehyde lead[44] to the formation of oxazolidinone (XXV).



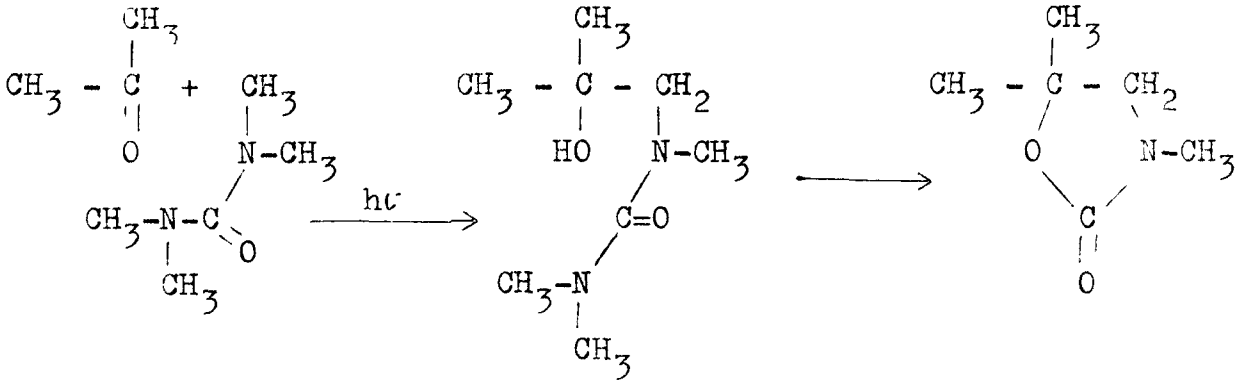
(XXV)

Steroidal oxazolidinone (XXVII) was reported[45] to be formed by the aziridine (XXVI) ring cleavage in HOAc containing $H_2N.NHCO_2Et$.

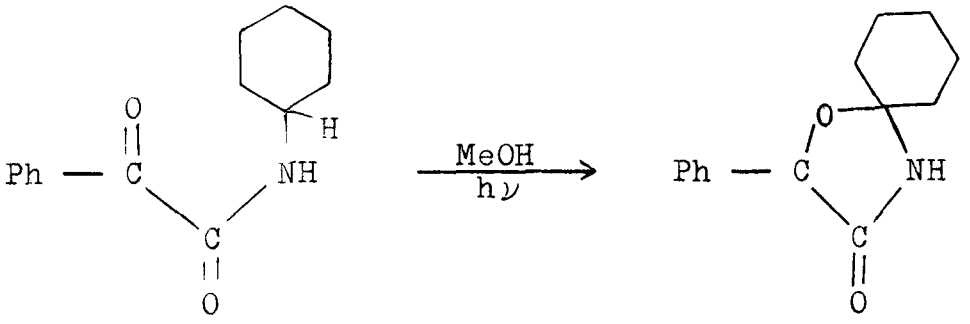


(XXVI) (XXVII)

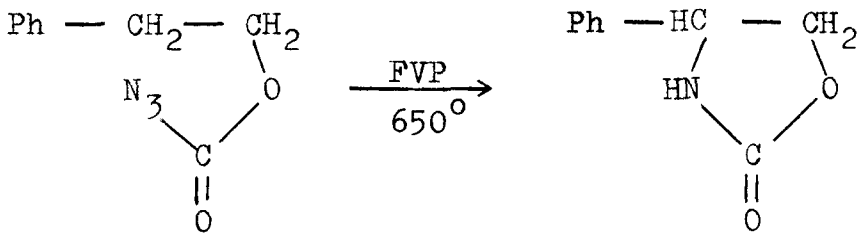
The photoreaction of tetramethylurea with acetone was reported[46] to give carbamate which was cyclized to give oxazolidinone (XXVIII). Hiromu et al.[47] have shown that when N-alkyl α-oxoamide was subjected to photolysis gave oxazolidinone (XXIX). Flash vacuum pyrolysis (FVP) of azidoformate at 650° was reported[48] to furnish oxazolidinone (XXX).



(XXVIII)

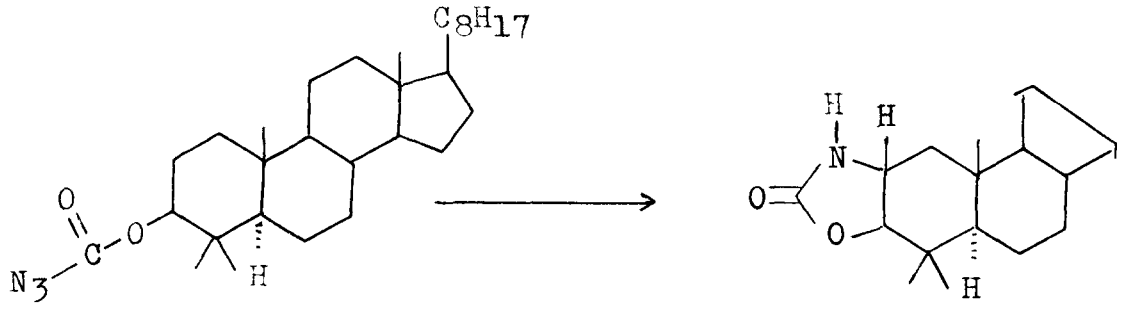


(XXIX)



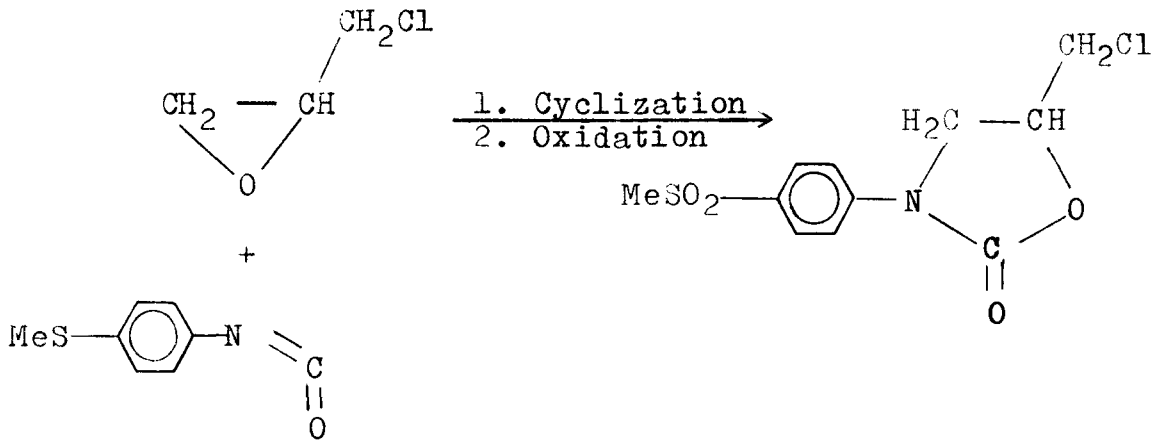
(XXX)

On thermolysis 3β-lanostanyl azidoformate (XXXI) gave[49] oxazolidinone (XXXII).



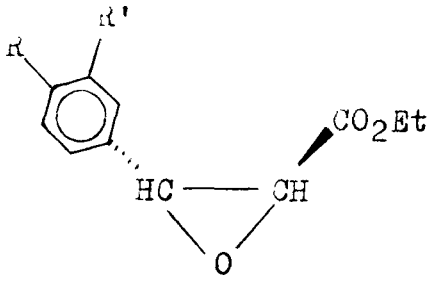
(XXXI) (XXXII)

Of the various methods developed to synthesize oxazolidinones, reaction of epoxide with isocyanate is an important one. Thus oxazolidinone (XXXIII) an antibacterial agent was prepared[50] by treating phenylisocyanate with epichlorohydrin followed by oxidation.

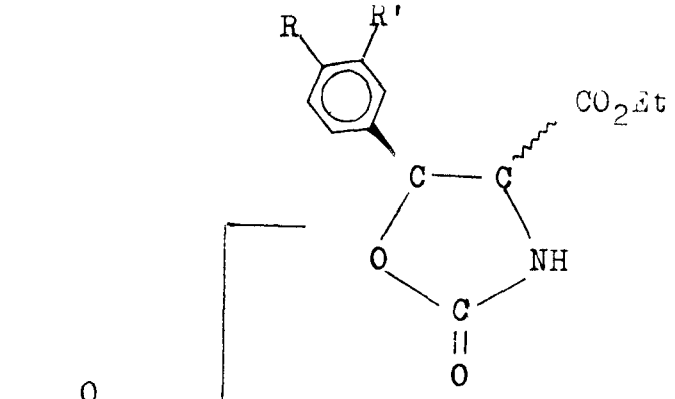


(XXXIII)

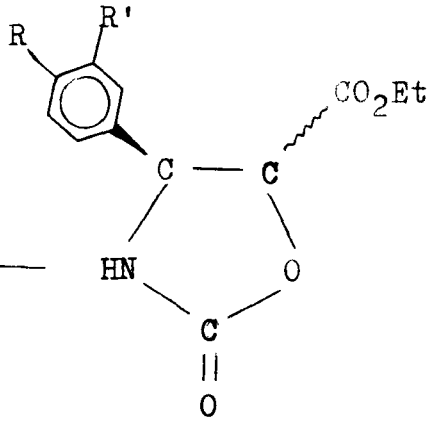
Recently Huth et al.[51] have shown the formation of cis and trans oxazolidinone (XXXVI and XXXVII) from the reaction of phenyloxirane (XXXIV) with urea. Oxazolidinones (XXXVIIA-D) useful as sedative, muscle relaxant and anxiolytics were also prepared[52] by cyclization of urea with the corresponding phenoxy-epoxypropane.



(XXXIV)



(XXXV)

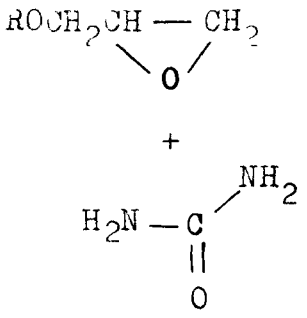


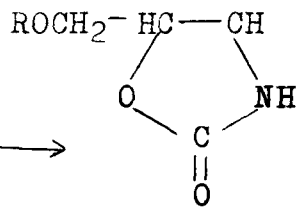
(XXXVI)

R = NO_2, Cl

R' = H

R = R' = H, MeO





(XXXVII) A - C_6H_5

(XXXVII) B - $C_6H_4CMe_3$

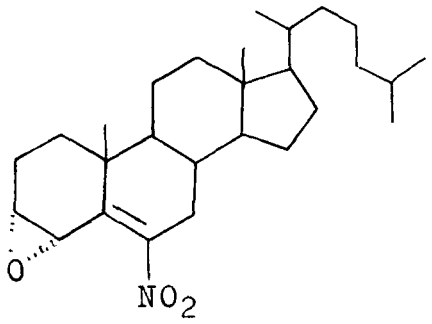
(XXXVII) C - $C_6H_3(CMe_3)_2$

(XXXVII) D - 2-allytertbutylphenyl

Discussion

After the discovery of biologically active steroids and their applications in chemotherapy, a large number of these compounds were screened for their biological potentials. The naturally occurring steroids containing oxygen or nitrogen or both have been found to be endowed with pronounced and specific biological activities. The interesting physiological properties of the steroidal compounds containing oxygen and nitrogen with useful therapeutic properties stimulated extensive research in this field and this resulted in the preparation of a veriety of such steroids with useful biological activities.

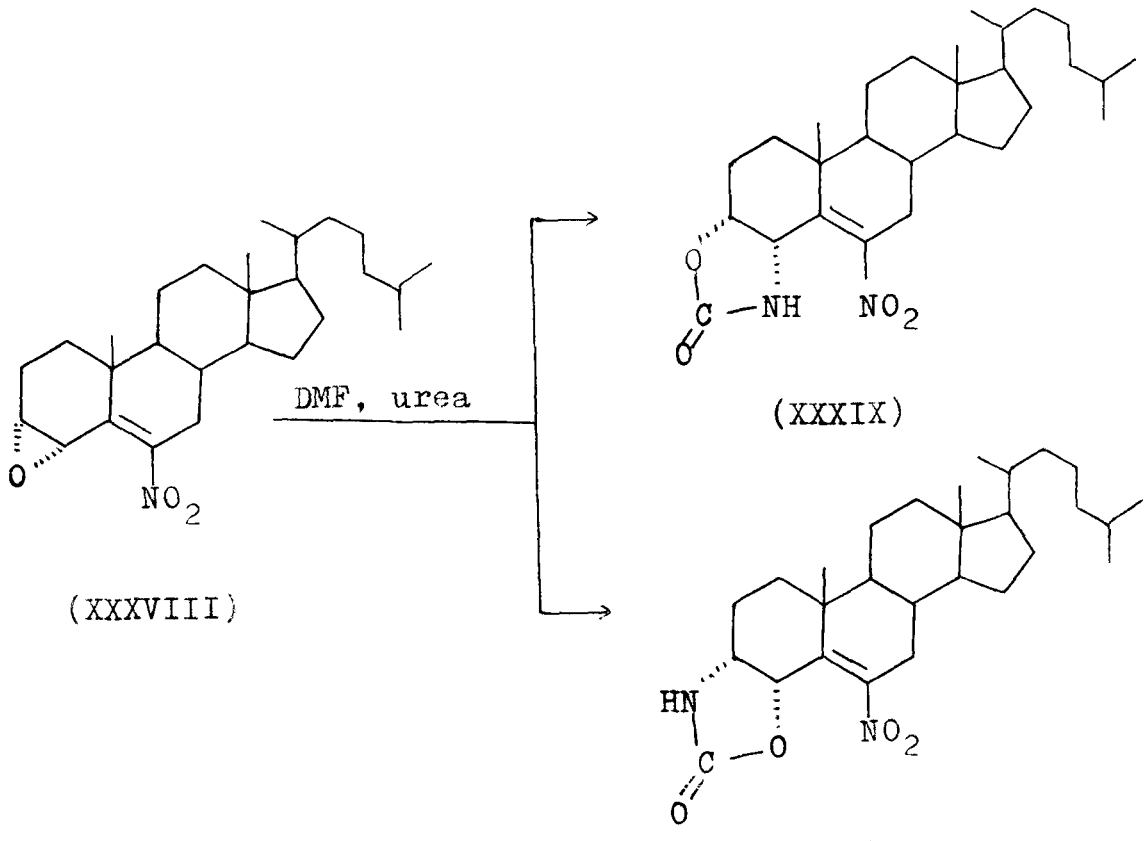
Oxazolidinone derivatives are a class of heterocyclic compounds containing oxygen and nitrogen and have been proved to possess a large number of biological activities such as antidepressant[53], antibacterial[50], fungicidal[7,8], herbicidal[54], analgesic[55], anti-inflammatory[53], muscle relaxant[52,53], anticonvulsant[52,56] and many more activities[35,52,57]. A survey of literature revealed that no significant work has been done concerning the synthesis of steroidal oxazolidinones, which are expected to possess enhanced biological activities. This prompted us to undertake the synthetic studies of steroidal oxazolidinones by the reaction of 3α,4α-epoxy-nitrocholest-5-ene (XXXVIII) with urea and acetamide.



(XXXVIII)

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (XXXVIII) with urea

3α,4α-Epoxy-6-nitrocholest-5-ene (XXXVIII) in N,N-dimethyl formamide was refluxed with urea for 6 hours. After the completion of the reaction, the reaction mixture was worked up in ether and dried. Evaporation of the solvent provided an oil which on column chromatography over silica gel lead to the separation of two compounds, m.p. 126° and 137°.



(XXXVIII)

(XXXIX)

(XL)

Characterization of the compound m.p. 126° as 6-nitrocholest-5-eno[4α,3α-d]oxazolidin-2'-one (XXXIX)

The compound m.p. 126° was analysed correctly for $C_{28}H_{44}N_2O_4$. The IR spectrum of compound exhibited a sharp band at 3490 (-NH) and another sharp band at 1715 cm^{-1} characteristic for the oxazolidinone moiety[58,59]. Other bands were at 1640 (C=C)[60], 1535 and 1375 cm^{-1} (C-NO_2)[60]. The NMR spectrum of the compound gave a sharp singlet integrating for one proton at δ 7.94 (disappeared on addition of D_2O) which was assigned to the amide proton (-N<u>H</u>). A multiplet centred at δ 5.15 integrating for one proton was ascribed to C3-β<u>H</u> ($W_{\frac{1}{2}}$ = 7Hz; equatorial). A doublet type peak which appeared at δ 4.27 was ascribed to C4-β<u>H</u> (J = 3Hz, pseudo axial). The methyl signals appeared at δ 1.21 (C10-C<u>H</u>$_3$), 0.68 (C13-C<u>H</u>$_3$), 0.93 and 0.83 (remaining methyl protons). On the basis of the above discussion the compound m.p. 126° was characterized as 6-nitrocholest-5-eno[4α,3α-d]oxazolidin-2'-one (XXXIX).

Characterization of the compound m.p. 137° as 6-nitrocholest-5-eno[3α,4α-d]oxazolidin-2'-one (XL)

The compound m.p. 137° was analysed correctly for $C_{28}H_{44}N_2O_4$. The IR spectrum of the compound gave band at 3420 cm^{-1}(broad;-NH). The band at 1725 cm^{-1} clearly indicated the formation of oxazolidinone[59]. The bands at 1650 (C=C), 1525 and 1365 cm^{-1}(C-NO_2) were observed. The NMR spectrum gave a sharp singlet integrating for one proton at δ 8.01 which was attributed to amide proton

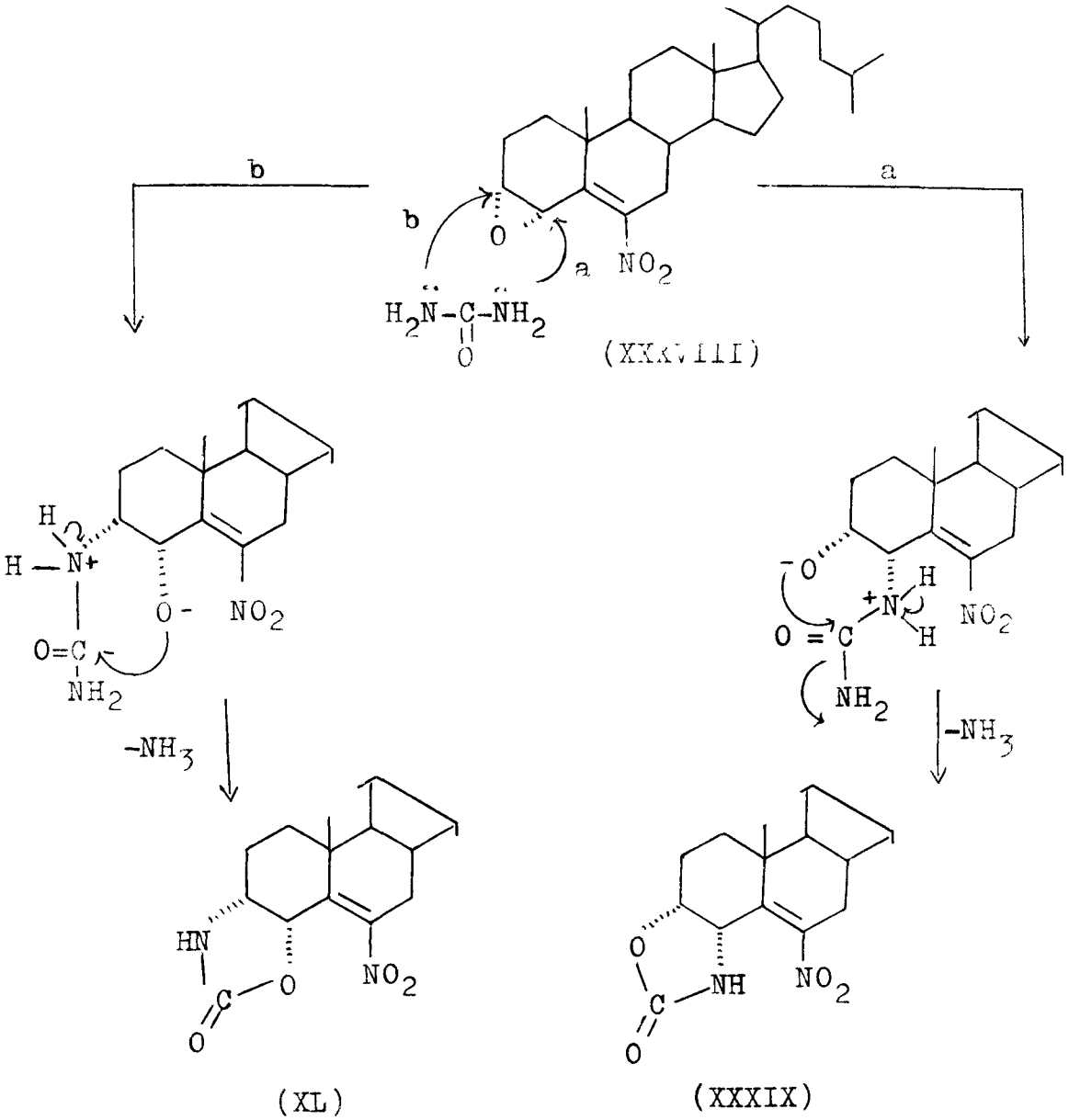
(-NH; exchangeable with D_2O) of the oxazolidinone ring. A doublet type peak for one proton appeared at δ 5.48, comparatively at lowfield was assigned to the C4-β$\underline{H}$ (J = 3Hz pseudo axial). The multiplet which appeared at a higher field at δ 3.98 was assigned to the C3-β$\underline{H}$ ($W_{\frac{1}{2}}$ = 7Hz, equatorial). The methyl signals were at δ 1.20 (C10-C$\underline{H}_3$), 0.66 (C13-C$\underline{H}_3$), 0.88 and 0.78 (remaining methyl protons). On the basis of the above discussion the compound m.p. 137° was characterized as 6-nitrocholest-5-eno[3α,4α-d] oxazolidin-2'-one (XL).

The distinction between (XXXXIX) and (XL) was made with out any ambiguity with the help of NMR spectra of these compounds. It is pertinent to mention here that both C3-β proton (equatorial) in (XXXIX) and C4-α proton (pseudo axial) in (XL) are attached to oxygen bearing carbon atoms, but C4-β proton though being axial[61] (pseudo) appears at lowerfield. Similar observation is made for protons at carbon atoms C3 and C4 which are attached to nitrogen in (XL) and (XXXIX) respectively. This can be attributed to the allylic nature of C4 carbon atom and also to the electron withdrawing nitrogen at C6.[61,62,63] Similar observations have been made earlier too.

Moreover a sharp singlet for -N$\underline{H}$ in both the cases (XXXIX and XL) clearly indicated that they are non-coupled. This is possible only when these protons (-NH) are at right angle[61] ($\angle 90^{\circ}$)

to the protons of adjacent carbon atoms (C3 and C4). This condition being satisfactorily fulfilled is seen with the help of drieding model, ofcourse with a certain amount of strain on the rings which is indicated by the pseudochair conformation.

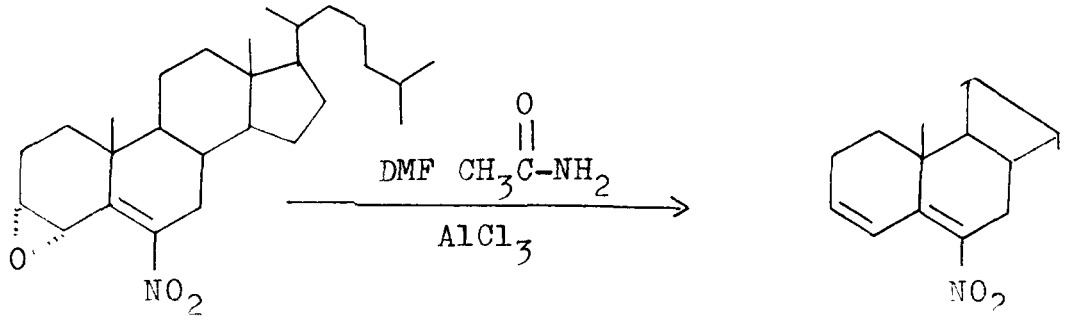
With the help of a tentative mechanism (Scheme-1) which involves the loss of ammonia the formation of (XXXIX) and (XL) can be explained.



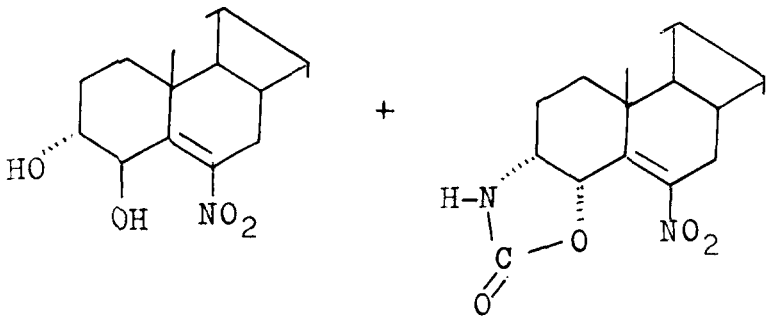
It may be mentioned here that Huth et al.[51] also have reported the formation of isomeric oxazolidinones from reaction of epoxide with urea with the elimination of ammonia.

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (XXXVIII) with acetamide- $AlCl_3$

3α,4α-Epoxy-6-nitrocholest-5-ene (XXXVIII) in N,N-dimethyl formamide when treated with acetamide ($AlCl_3$ was added as a catalyst) provided three compounds m.p. 72°, 120° and 137°.



(XXXVIII) (XLI)



(XLII) (XL)

Characterization of the compound, m.p. 72° as 6-nitrocholesta-3,5-diene (XLI)

The compound m.p. 72° (reported[64] m.p. 72°) was analysed for $C_{27}H_{43}NO_2$. Its IR spectrum showed absorption bands at 1680 (-C=C-C=C-)[60], 1508 and 1380 cm^{-1} (C-NO_2). In NMR spectrum the C4 proton was observed at δ 6.5 as a doublet (J = 10Hz). The C3-proton appeared as a multiplet at δ 6.1. Methyl signals were observed at δ 1.08 (C10-C$\underline{H}_3$), 0.7 (C13-C$\underline{H}_3$), 0.95 and 0.83 (remaining methyl protons). The compound was found identical(t.l.c., m.p., m.m.p., i.r. and n.m.r.) with 6-nitrocholesta-3,5-diene (XLI).

Characterization of the compound m.p. 120° as 3α,4β-dihydroxy-6-nitrocholest-5-ene (XLII)

The compound m.p. 120° was analysed for $C_{27}H_{45}NO_4$. The presence of hydroxy groups is well revealed by the band at 3410 cm^{-1} (strong, broad). The other characteristic bands were at 1640 (C=C), 1530 and 1370 cm^{-1} (C-NO_2)[60]. In its NMR spectrum a doublet type signal appeared at δ 4.45 intigrating for one proton was assigned to C4-α$\underline{H}$ (J = 3Hz; equatorial). The C3-β$\underline{H}$ appeared as a multiplet at δ 4.06 ($W_{\frac{1}{2}}$ = 7Hz; equatorial). The appearance of C4-α$\underline{H}$ comparatively at downfield than C3-β$\underline{H}$, may once again be attributed to C4 allylic carbon atom and to electron withdrawing nitro group at C6. The hydroxyl protons appeared at

δ 2.65 (exchangeable with D_2O) and the methyl proton appeared at δ 1.20 (C10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons). In the light of the above discussion the compound m.p. 120°, may therefore be regarded as 3α,4β-dihydroxy--6-nitrocholest-5-ene (XLII).

Characterization of compound m.p. 137° as 6-nitrocholest-5-eno [3α,4α-d]oxazolidin-2'-one (XL)

The compound m.p. 137° was analysed for $C_{28}H_{44}N_2O_4$. The IR spectrum showed bands at 3420 (-N$\underline{H}$), 1725 (oxazolidinone ring), 1650 (C=C), 1525 and 1365 cm^{-1} (C-NO_2). The NMR spectrum gave a signal for one proton at δ 8.01 (-N$\underline{H}$; exchangeable with D_2O). A doublet for one proton appeared at δ 5.48 (C4-β$\underline{H}$, J = 3Hz; pseudo axial) anda multiplet appeared at δ 3.98 (C3-β$\underline{H}$, $W_{\frac{1}{2}}$ = 7Hz; equatorial). The methyl signals appeared at δ 1.20 (C10-C$\underline{H}_3$), 0.66 (C13-C$\underline{H}_3$), 0.88 and 0.78 (remaining methyl protons). On the basis of these data the compound m.p. 137° was found to be 6-nitrocholest-5-eno[3α,4α-d]oxazolidin-2'-one (XL) [identical with the one (XL) which was obtained by the reaction of urea and the epoxide (XXXVIII)].

Experimental

3β-Acetoxycholest-5-ene

A mixture of cholesterol (50 g) pyridine (75 ml, freshly, distilled over KOH) and freshly distilled acetic anhydride (50 ml) was heated on a water bath for 2 hours. The reaction mixture was poured on to crushed ice-water mixture with stirring. A light brown solid was obtained which was filtered under suction, washed with water until free from pyridine and air dried. The crude product on recrystallization from acetone gave pure 3β-acetoxycholest-5-ene (45.0 g), m.p. 114-115° (reported[65] m.p.116°).

3β-Acetoxy-6-nitrocholest-5-ene

3β-Acetoxycholest-5-ene (10 g) was covered with nitric acid (250 ml, d, 1.52) and sodium nitrite (10.0 g) was gradually added over a period of one hour with continuous stirring. Slight cooling was also required during the course of the reaction. Stirring was continued for additional two hours. A yellow spongy mass separated on the surface of the mixture. The mixture was diluted with cold water (250 ml). A green coloured solution was obtained. The whole mass was extracted with ether and washed successively with water, sodium bicarbonate solution (5%) and water. The ethereal solution was then dried over anhydrous sodium sulphate and filtered. Removal of the solvent provided an oil which was recrystallized from methanol to yield 3β-acetoxy-6-nitrocholest-

5-ene, (6.8 g), m.p. 103° (reported[66] m.p. 102-104°).

6-Nitrocholesta-3,5-diene

3β-Acetoxy-6-nitrocholest-5-ene (10.0 g) was dissolved in N,N-dimethyl formamide (50 ml) and sodium azide (5.0 g) was added gradually with shaking. The reaction mixture was left at room temperature for 2 days. It was diluted with water and extracted with ether. The ethereal layer was washed with water, and dried over sodium sulphate (anhydrous). Removal of the solvent gave an oily residue which was chromatographed over silica gel. Elution with light petroleum ether:ether (40:1) furnished 6-nitrocholesta-3,5-diene (8.0 g) which was crystallized from light petroleum ether, m.p. 72° (reported[64] m.p. 72°).

Analysis Found : C, 78.41; H, 10.45; N, 3.36

$C_{27}H_{43}NO_2$ requires : C, 78.45; H, 10.41; N, 3.38%

IR : $\nu_{max.}$ 1680 (C=C-C=C), 1508 and 1380 cm^{-1} ($C-NO_2$)

NMR : δ 6.5 d(C4-H, J = 10Hz), 6.1 mc(C3-H), 1.08(C10-CH_3), 0.70(C13-CH_3), 0.95 and 0.83 (remaining methyl protons).

3α,4α-Epoxy-6-nitrocholest-5-ene (XXXVIII)

6-Nitrocholesta-3,5-diene (10.0 g) in chloroform (35 ml) was treated with m-chloroperbenzoic acid (7.0 g) and left at -8° for 24 hours. The mixture was then washed with ice-cold sodium bicarbonate solution (5%), sodium thiosulphate solution (5%) and water. It was dried over sodium sulphate. Removal

of the solvent gave an oily residue which was chromatographed over a column of silica gel. Elution with petroleum ether:ether (30:1) provided the epoxide (XXXVIII) which was crystallized from petroleum ether (7.0 g) m.p. 101° (reported[67] m.p. 101°).

Analysis Found : C, 75.49; H, 10.00; N, 3.24

$C_{27}H_{43}NO_3$ requires : C, 75.52; H, 10.02; N, 3.26%

IR : $\nu_{max.}$ 1260(C—C), 1650(C=C), 1510 and 1375 cm^{-1} ($C-NO_2$)

NMR : δ 3.23 br,m(C3-β$\underline{H}$; $W_{\frac{1}{2}}$ = 6Hz, equatorial), 3.63 d (C4-β$\underline{H}$, J = 3Hz, pseudo axial), 1.05 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.81 and 0.91 (remaining methyl protons).

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (XXXVIII) with urea: 6-Nitrocholest-5-eno[4α,3α-d]oxazolidin-2'-one (XXXIX) and 6-nitrocholest-5-eno[3α,4α-d]oxazolidin-2'-one (XL)

3α,4α-Epoxy-6-nitrocholest-5-ene (XXXVIII) (1.5 g) in N,N-dimethyl formamide (25 ml) was refluxed with urea (1.5 g) for about 6 hours. After the completion of the reaction, it was extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate. Evaporation of the solvent provided an oil which was chromatographed over a column of silica gel. Elution with petroleum ether:ether (8:1) provided a solid (XXXIX) crystallized from petroleum ether (400 mg), m.p. 126°.

Analysis Found : C, 71.09; H, 9.32; N, 5.88

$C_{28}H_{44}N_2O_4$ requires : C, 71.18; H, 9.32; N, 5.92%

IR : $\nu_{max.}$ 3490 s(-NH), 1715 (oxazolidinone moiety), 1640(C=C), 1535 and 1375 cm^{-1} (C-NO_2).

NME : δ 7.94 s(-N<u>H</u>; exchangeable with D_2O), 5.15 mc(C3-β<u>H</u>, $W_{\frac{1}{2}}$ = 7Hz; equatorial), 4.27 d(C4-β<u>H</u>, J = 3Hz; pseudo axial , 1.21 (C10-C<u>H</u>$_3$), 0.68 (C13-C<u>H</u>$_3$), 0.93 and 0.83 (remaining methyl protons).

Further elution with petroleum ether:ether (4:1) furnished (XL) crystallized from petroleum-ether (300 mg) m.p. 137°.

Analysis Found : C, 71.30; H, 9.25; N, 5.80

$C_{28}H_{44}N_2O_4$ requires : C, 71.18; H, 9.32; N, 5.93%

IR : $\nu_{max.}$ 3420 br(-NH), 1725 (oxazolidinone moiety), 1650(C=C), 1525 and 1365 cm^{-1} (C-NO_2)

NMR : δ 8.01 s(-NH; exchangeable with D_2O), 5.48 d(C4-β<u>H</u>; J = 3Hz, pseudo axial), 3.98 mc(C3-β<u>H</u>, $W_{\frac{1}{2}}$ = 7Hz, equatorial), 1.20(C10-C<u>H</u>$_3$), 0.66(C13-C<u>H</u>$_3$), 0.88 and 0.78 (remaining methyl protons).

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (XXXVIII) with acetamide-$AlCl_3$: 6-Nitrocholesta-3,5-diene (XLI), 3α,4β-dihydroxy-6-nitrocholest-5-ene (XLII) and 6-nitrocholest-5-eno [3α,4α-d]oxazolidin-2'-one (XL)

3α,4α-Epoxy-6-nitrocholest-5-ene (XXXVIII) (1.5 g) in N,N-dimethyl formamide (30 ml) was refluxed with acetamide (1.5 g) and $AlCl_3$ (0.25 g) for about 6 hours. After the completion of the reaction, it was extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate. Evaporation of the solvent provided an oil which was chromatographed over silica gel. Elution with petroleum ether:ether (40:1) provided 6-nitrocholesta-3,5-diene (XLI) (100 mg), m.p.72° (reported[64] m.p. 72°).

Analysis Found : C, 78.41; H, 10.45; N, 3.36

$C_{27}H_{43}NO_2$ requires : C, 78.45; H, 10.41; N, 3.38%

IR : ν max. 1680 (C=C-C=C), 1508 and 1380 cm^{-1} ($C-NO_2$)

NMR : δ 6.5 d(C4-H, J = 10Hz), 6.1 mc(C3-H), 1.08(C10-CH_3), 0.70(C13-CH_3), 0.95 and 0.83 (remaining methyl protons).

Further elution with petroleum ether:ether (8:1) provided compound (XLII) (300 mg) recrystallized from light petroleum ether, m.p. 120°.

Analysis Found : C, 72.50; H, 10.01; N, 3.18

$C_{27}H_{45}NO_4$ requires : C, 72.48; H, 10.06; N, 3.13%

IR : ν max. 3410 (-OH), 1640 (C=C), 1530 and 1370 cm^{-1}($C-NO_2$)

NMR : δ 4.45 d(C4-α$\underline{H}$, J = 3Hz; equatorial), 4.06 mc(C3-β$\underline{H}$, $W_{\frac{1}{2}}$ = 7Hz; equatorial), 2.65 (-O$\underline{H}$), 1.20 (C10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons).

Further elution with petroleum ether:ether (4:1) yielded the compound (XL) (300 mg) recrystallized from light petroleum ether, m.p. 137°, which was found identical in all respects with compound (XL) obtained by the reaction of 3α,4α-epoxide (XXXVIII) with urea.

Analysis Found : C, 71.30; H, 9.25; N, 5.80

$C_{28}H_{44}N_2O_4$ requires : C, 71.18; H, 9.32; N, 5.93%

IR : $\nu_{max.}$ 3420 (-N$\underline{H}$), 1725 (oxazolidinone ring), 1650 (C=C), 1525 and 1365 cm^{-1} (C-NO_2).

NMR : δ 8.01 (-N$\underline{H}$; exchangeable with D_2O), 5.48 d(C4-β$\underline{H}$, J=3Hz; pseudo axial), 3.98 mc(C3-β$\underline{H}$, $W_{\frac{1}{2}}$ = 7Hz; equatorial), 1.20 (C10-C$\underline{H}_3$), 0.66 (C13-C$\underline{H}_3$), 0.88 and 0.78 (remaining methyl protons).

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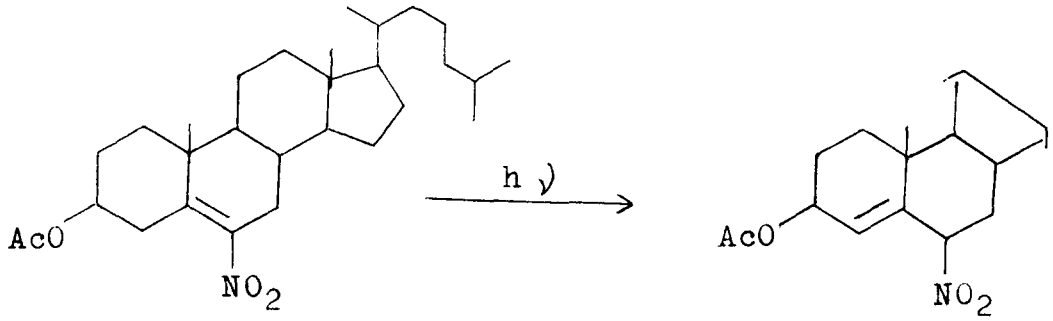
Part Three

Reduction of Steroidal Nitroolefins

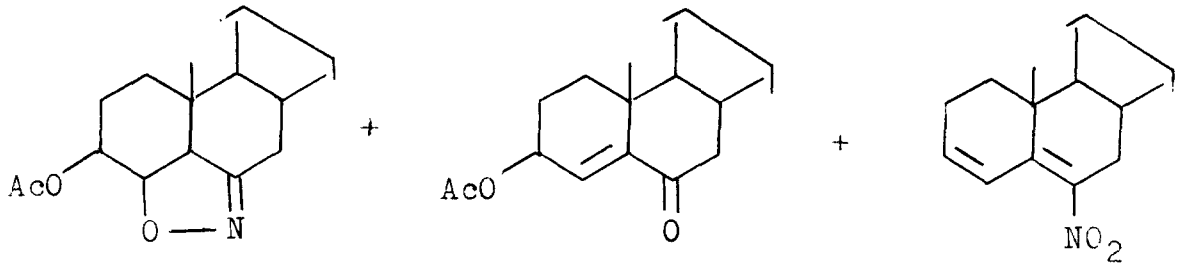
Theoretical

In the recent years syntheses of steroidal compounds have gained importance because of their biological activities associated with them. Reduction is one among the various reactions used in the synthetic pathway. Many types of reagents which have been successfully employed for this purpose are hydrogen with metal, lithium aluminium hydride, zinc-acetic acid, sodium borohydride and other metallic hydrides. Photochemical and electrochemical methods were also employed for reduction. Raney nickel catalysed reduction has not been studied thoroughly. To be very concise, in this chapter, attempts have been made to review the various reagents used in the reduction of steroidal nitro compounds.

It has been reported[1-3] that the irradiation of 3β-acetoxy-6-nitrocholest-5-ene (I) in hexane gave 6β-nitrocholest-4-en-3β-yl acetate (II) along with other products (III, IV and V).

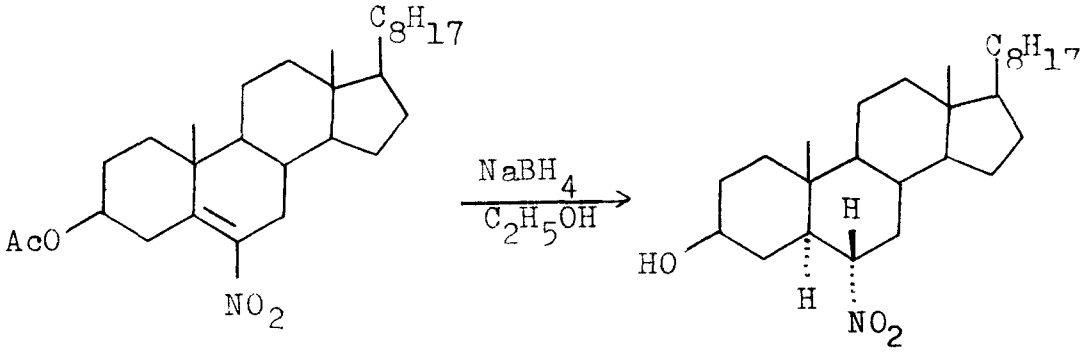


(I) (II)

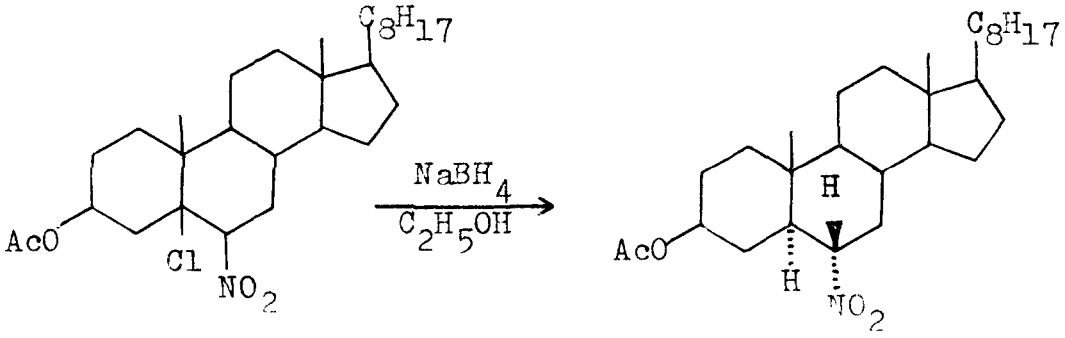


(III) (IV) (V)

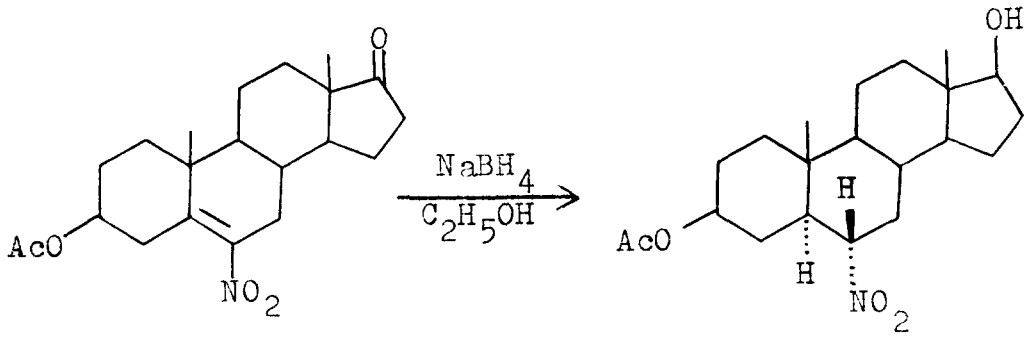
Steroidal nitro compounds (I, VII and IX) have been reported to give 6α-nitrosteroids (VI, VIII and X)[4], on reduction with sodium borohydride in ethanol.



(I) (VI)

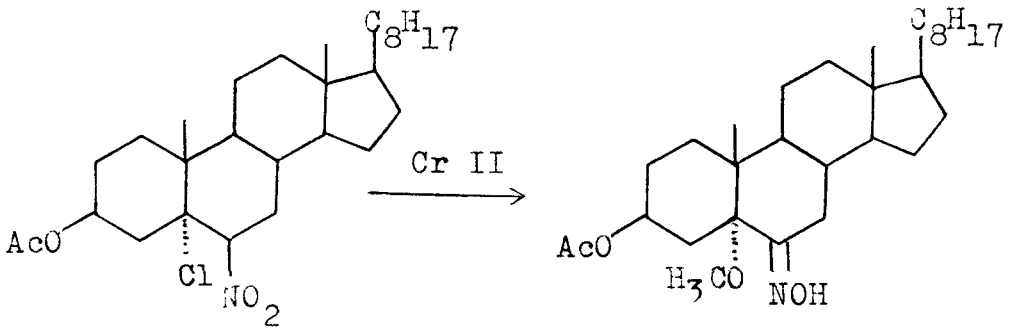


(VII) (VIII)



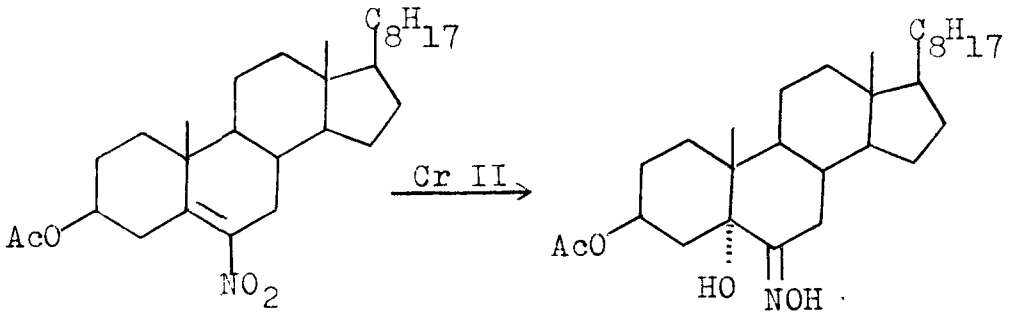
(IX) (X)

Hassner and Heathcock[4] have also reported that 3β-acetoxy-5α-chloro-6-nitrocholestane (XI) when treated with chromous chloride in methanolic hydrochloric acid gave 3β-acetoxy-5α-methoxy-6-oximinocholestane (XII).



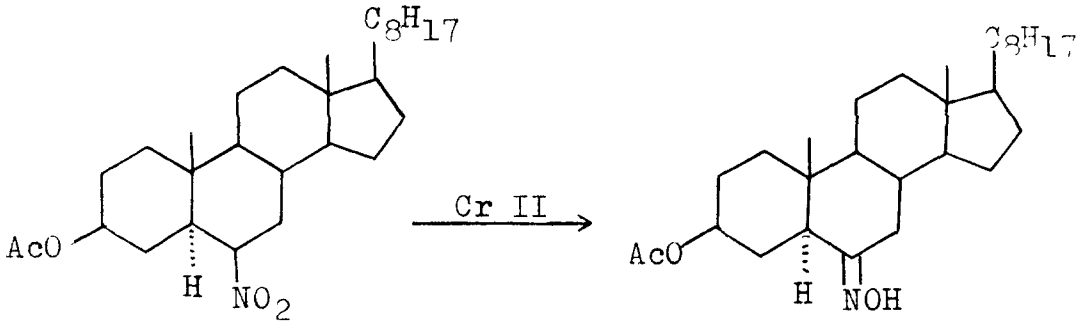
(XI) (XII)

Hanson and Premuzic[5] have reported the formation of 5α-hydroxy oxime (XIII) from 3β-acetoxy-6-nitrocholest-5-ene (I) when the latter was subjected to chromous chloride reduction.



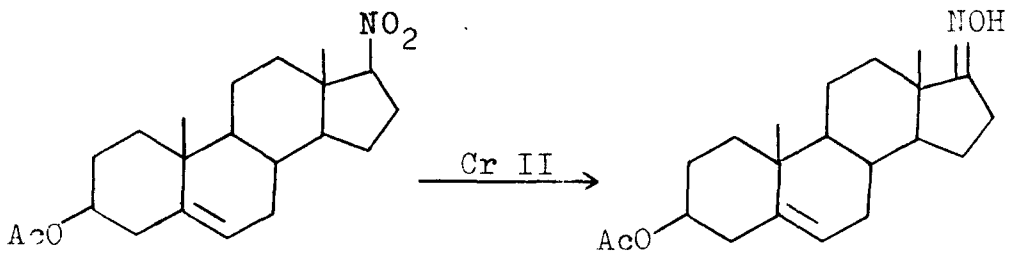
(I) (XIII)

When the reduction of 3β-acetoxy-6β-nitro-5α-cholestane (XIV) was carried out with acidic chromium (II) chloride, 6-oxy-[illegible]-cholestan-3β-yl-acetate(XV) was obtained[6].

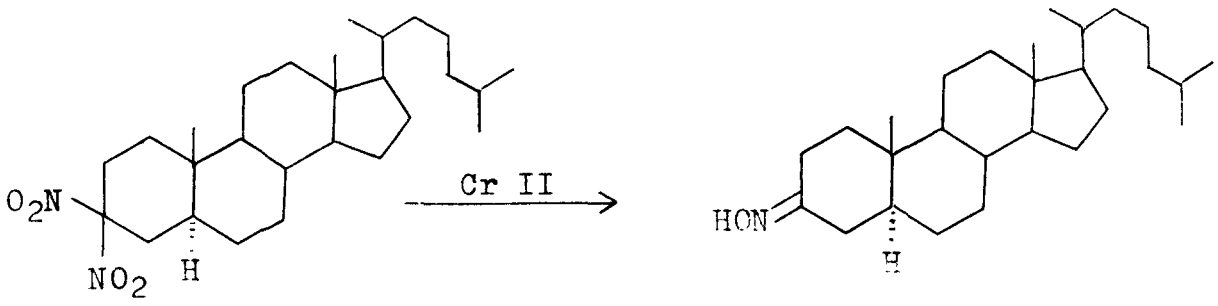


(XIV) (XV)

3β-Acetoxy-17β-nitroandrost-5-ene (XVI) when reduced with acidic chromium(II)chloride provided oxime (XVII)[6]. 6,3-Dinitro-5α-cholestane (XVIII) under similar reaction conditions was reduced to [illegible]-oxime (XIX)[6].

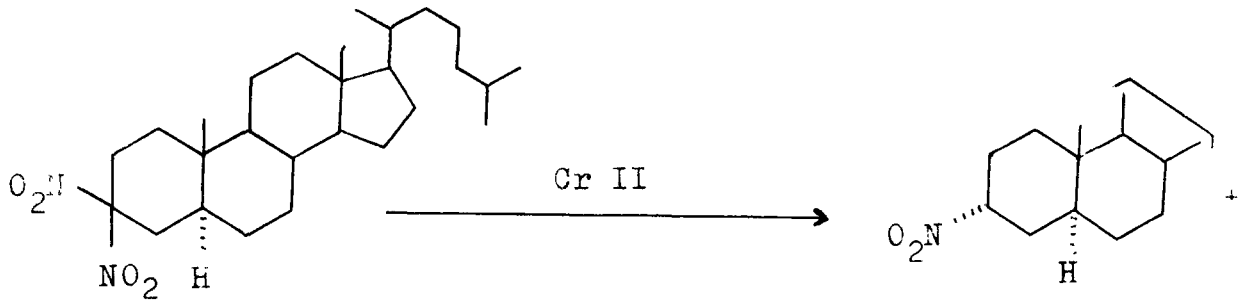


(XVI) (XVII)

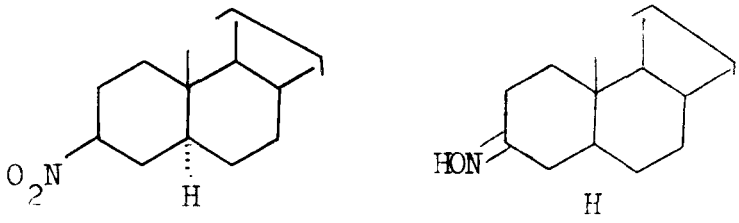


(XVIII) (XIX)

3,3-Dinitro-5α-cholestane (XVIII) on reduction gave a mixture of 3α- and 3β-nitro-5α-cholestanes (XVIIIa and b) and the 3-oxime (XIX) was also formed in a little amount[7].

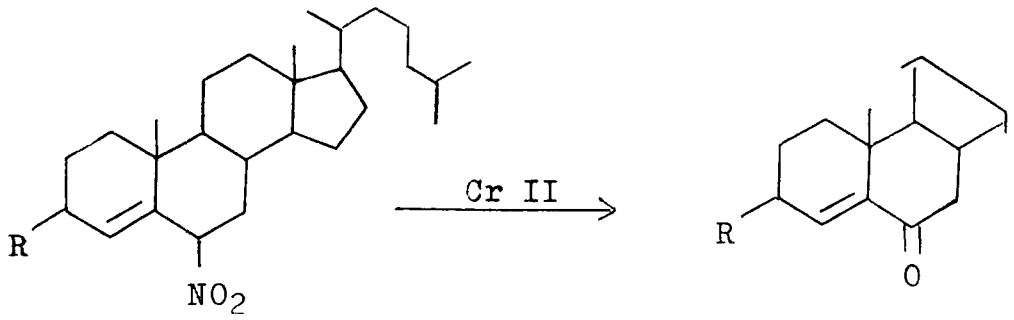


(XVIII) (XVIIIa)

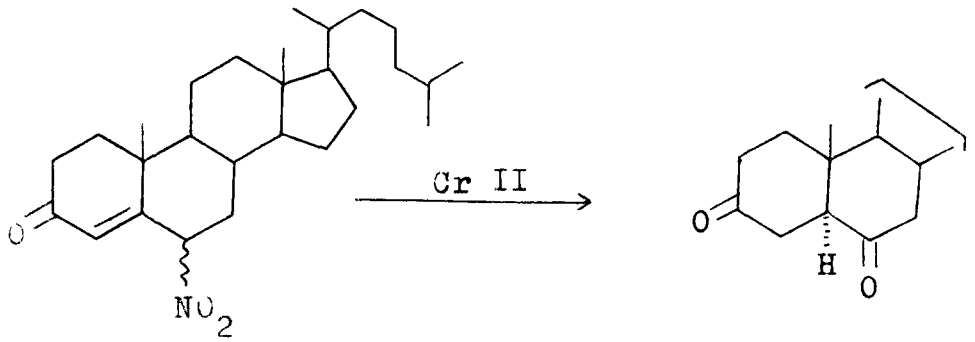


(XVIIIb) (XIX)

In contrast to the above cases chromium(II) chloride reduction of β,γ-unsaturated nitro steroids, 3β-acetoxy-6-nitrocholest-4-ene (XXa) and 3β-hydroxy-6-nitrocholest-4-ene (XXb) afforded the ketones, 3β-acetoxy-4-en-6-one (XXIa) and cholest-4-en-6-one (XXIb), rather than the oximes. Reduction of both 6α- and 6β-nitrocholest-4-en-3-ones (XXII) provided 3,6-dione (XXIII)[6].

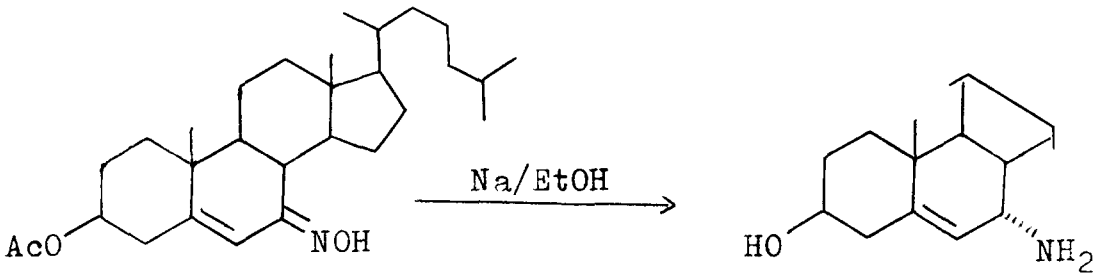


	R		R
(XXa)	-OAc	(XXIa)	-OAc
(XXb)	-OH	(XXIb)	-H

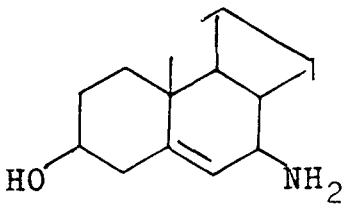


(XXII) (XXIII)

Reduction of the oxime of 7-ketocholesteryl acetate (XXIV) with sodium and ethyl alcohol gave 7α- and 7β-amino cholesterols (XXVa and XXVb)[8].

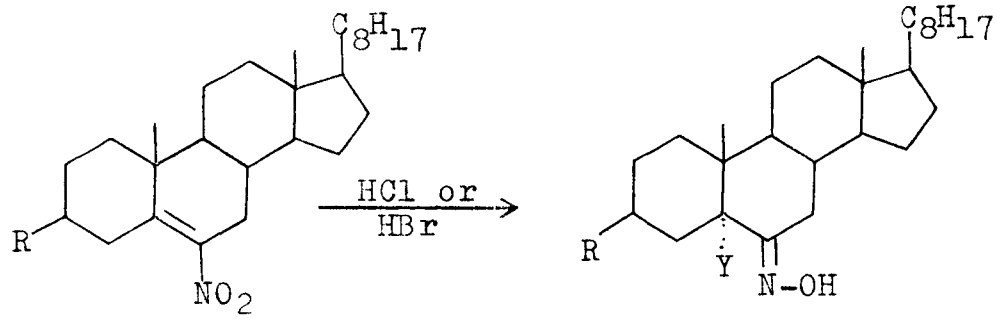


(XXIV) (XXVa)



(XXVb).

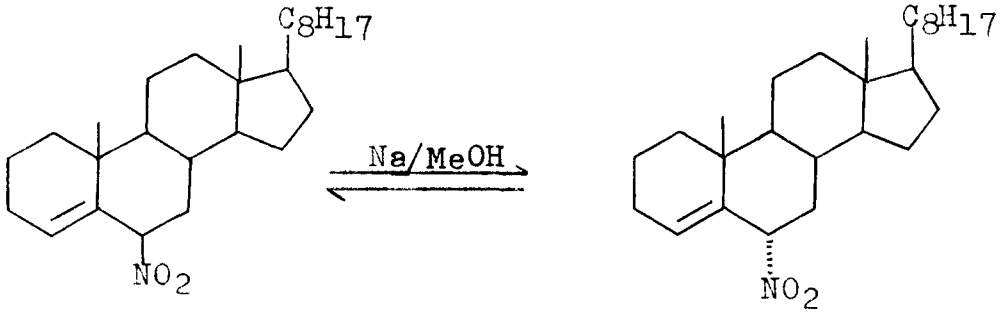
Yoshihisa et al.[9] found that the treatment of 6-nitro-cholest-5-enes (I, XXVII and XXIX) with dry hydrogen-chloride or bromide produces hitherto unaccessible 5α-chloro- or 5α-bromo-6-oximino-5α-cholestanes (XXVI , XXVIII, XXX and XXXI) in high yield.



	R
(I)	-OAc
(XXVII)	-Cl
(XXIX)	-H

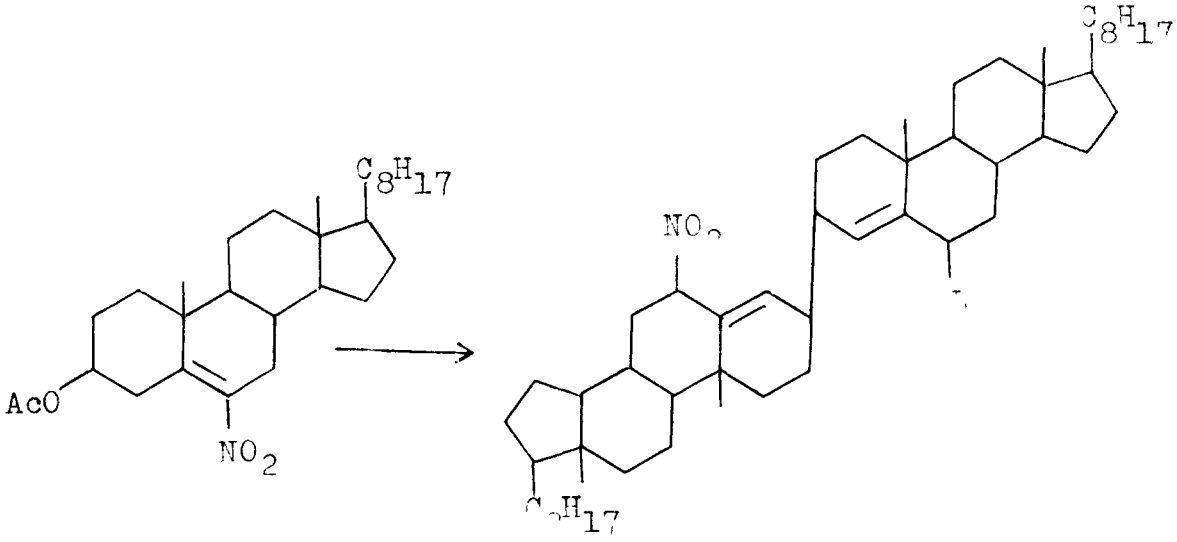
	R	Y
(XXVI)	-OAc,	-Cl
(XXVIII)	-Cl ,	-Cl
(XXX)	-H,	-Cl
(XXXI)	-OAc,	-Br

Pinhey et al.[10] reported that the treatment of 6β-nitro-cholest-4-ene (XXXII) with catalytic amount of sodium methoxide in methanol gave an equilibrium mixture which contained the starting material (XXXII) and the 6α-epimer (XXXIII) in a 1:1 ratio. According to them 6α-nitro steroid is thermodynamically more stable than its 6β-epimer.

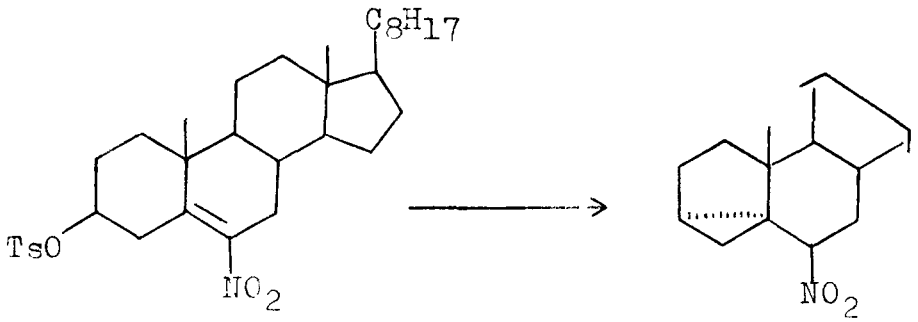


(XXXII) (XXXIII)

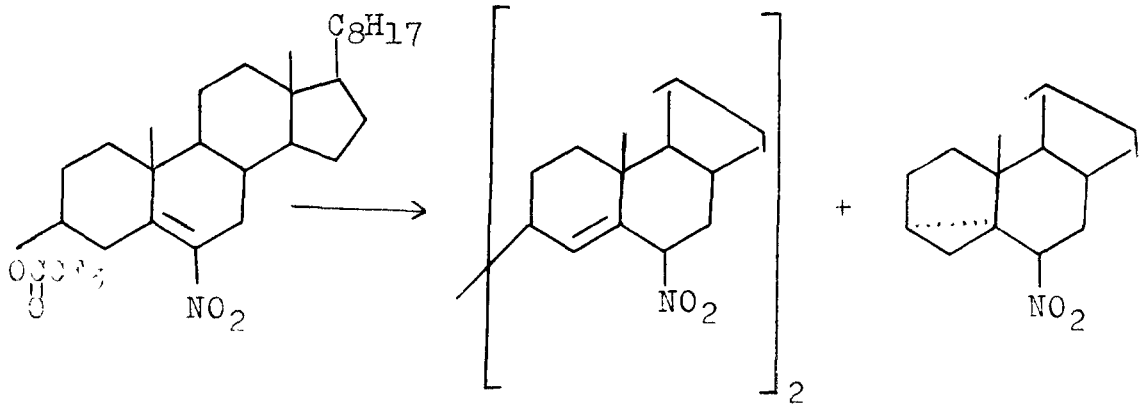
Sato and coworkers[11] carried out the reduction of homoallylic nitroesters in anhydrous DMF containing tetrabutylammonium perchlorate (TBAP) using platinum electrodes, during which 3β-acetoxy-6-nitrocholest-5-ene (I) gave a 3,3'-dimer (XXXIV) and 3β-tosylate-(XXXV) gave a cyclo steroid (XXXVI), 6β-nitro-3α-5-cyclo-5α-cholestan .3-Trifluoroacetate (XXXVII) showed intermediate behaviour and gave both the dimer (XXXIV) and cyclo steroid (XXXVI). Similarly, 6-nitrocholest-5-ene-3β,19-diol-3-acetate 19-tosylate (XXXVIII) gave 5β,19-cyclosteroid (XXXIX).



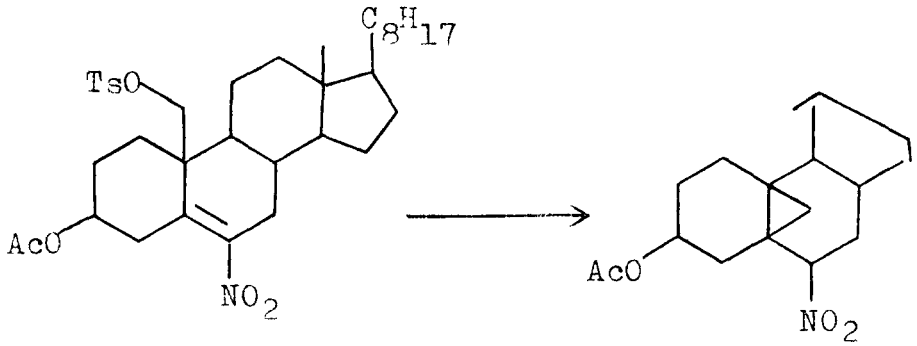
(I) (XXXIV)



(XXXV) (XXXVI)

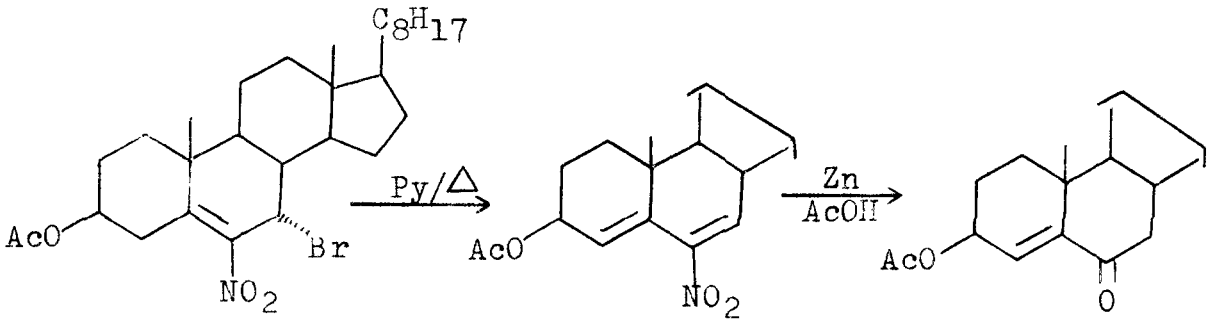


(XXXVII) (XXXIV) (XXXVI)

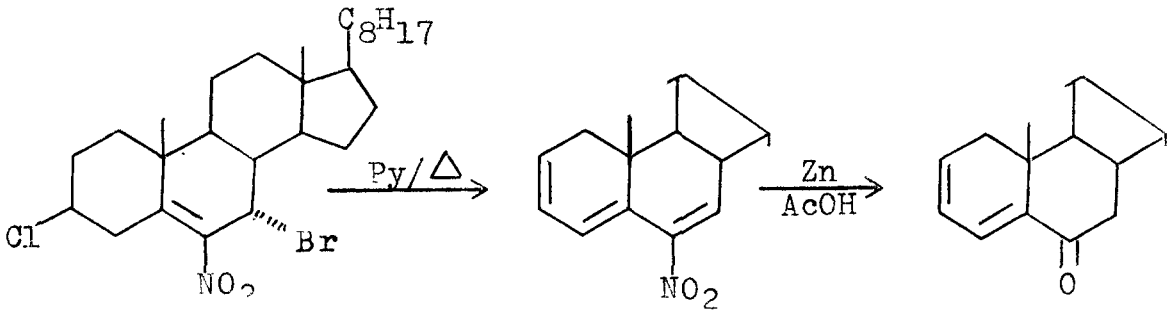


(XXXVIII) (XXXIX)

Treatment of (XL and XLIII) with pyridine under reflux provided the dehydrobrominated compounds (XLI and XLIV) which on Zn/AcOH reduction resulted in the formation of the respective ketones (XLII and XLV)[12].

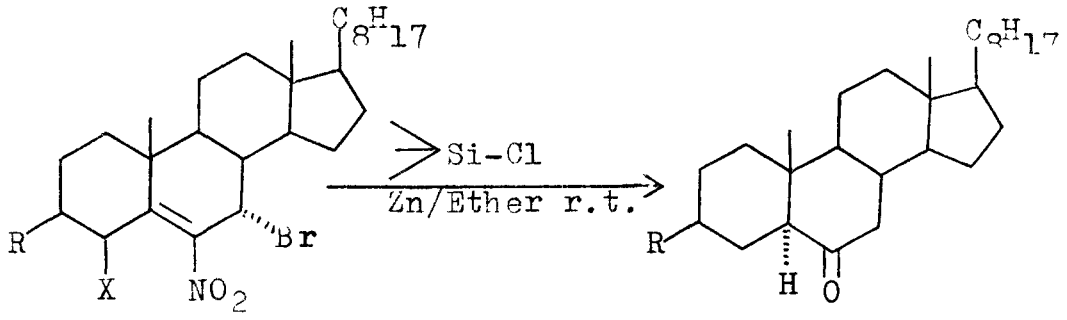


(XL) (XLI) (XLII)



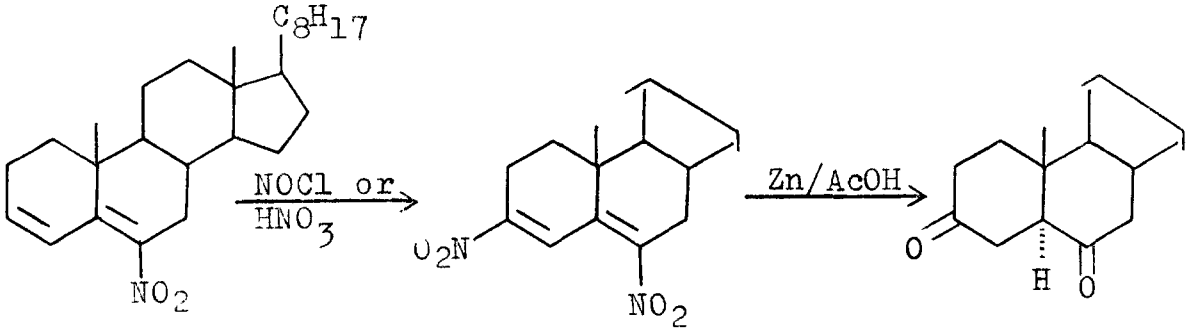
(XLIII) (XLIV) (XLV)

The utility of chlorotrimethylsilane was well [illegible] in reducing the bromonitro steroids (XL, XLIII and XLVIII) to the steroidal 6-ketones (XLVI, XLVII and XLIX)[13].



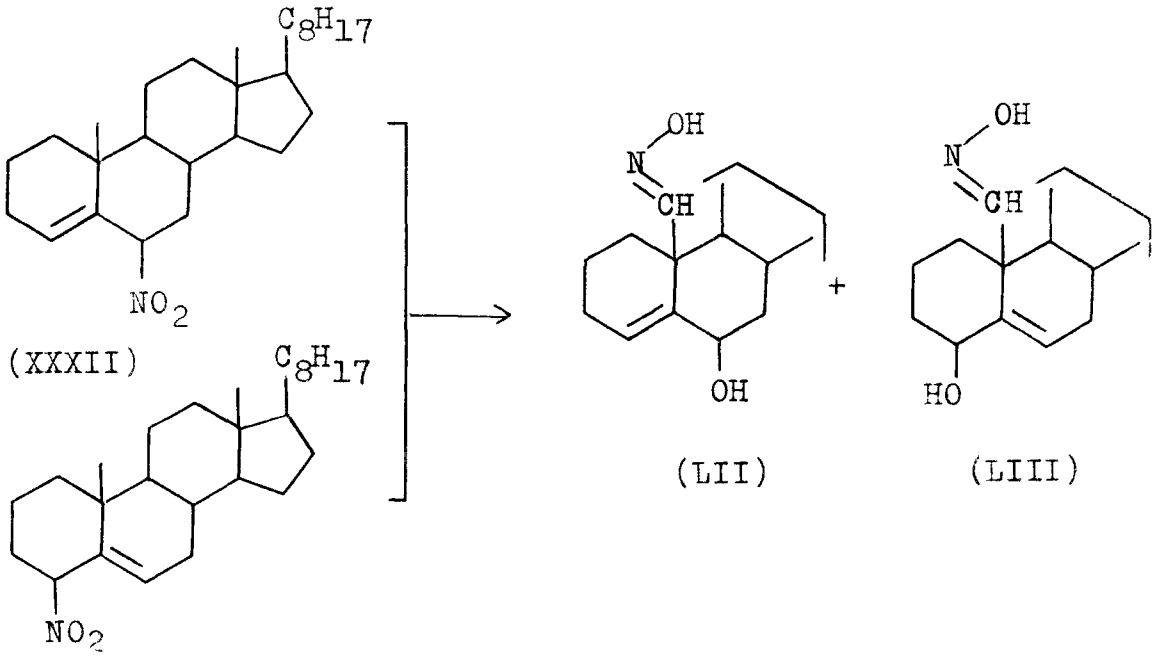
	R	X		R
(XL)	-OAc	-H	(XLVI)	-OAc
(XLIII)	-Cl	-H	(XLVII)	-Cl
(XLVIII)	-H	-Br	(XLIX)	-H

3,6-Dinitrocholesta-3,5-diene (L) obtained either by the reaction of NOCl or HNO_3 with 6-nitrocholesta-3,5-diene (V) on Zn/AcOH reduction furnished 3,6-dione (XXV)[14].

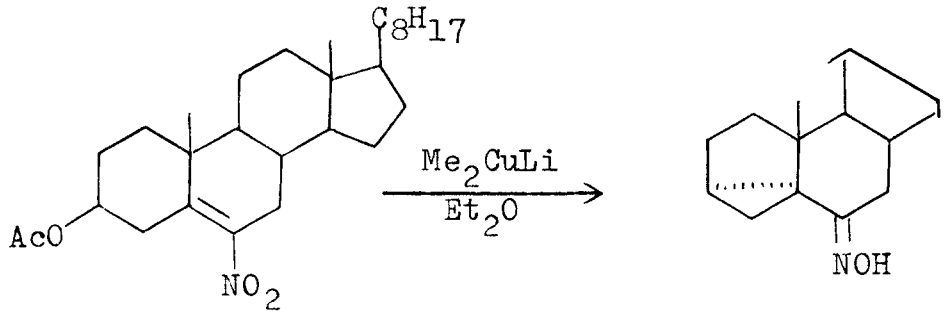


(V) (L) (XXV)

Photolysis of both 6β-nitrocholest-4-ene (XXXII) and 4β-nitrocholest-5-ene (LI) gave a mixture of hydroxyimino cholestenols (LII and LIII). This was reported to arise from a photochemical nitro-nitrosooxy rearrangement followed by Barton reaction[15].

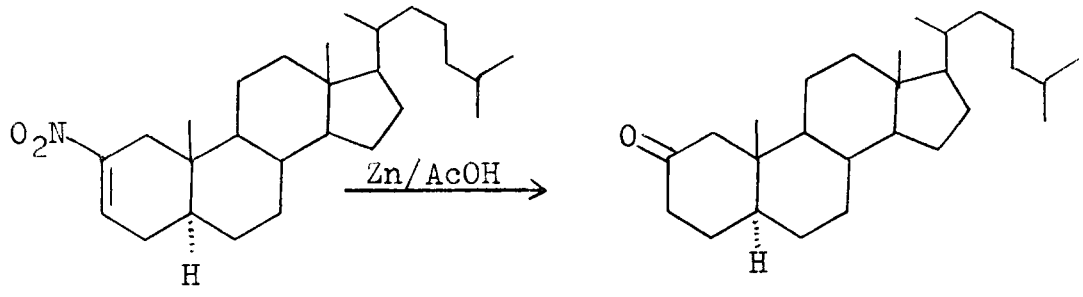


Stiver and Yates[16] reported that the treatment of 3β-acetoxy-6-nitrocholest-5-ene (I) with excess of lithium dimethylcuprate in ether gave 3α,5α-cyclocholestan-6-one oxime (LIV).



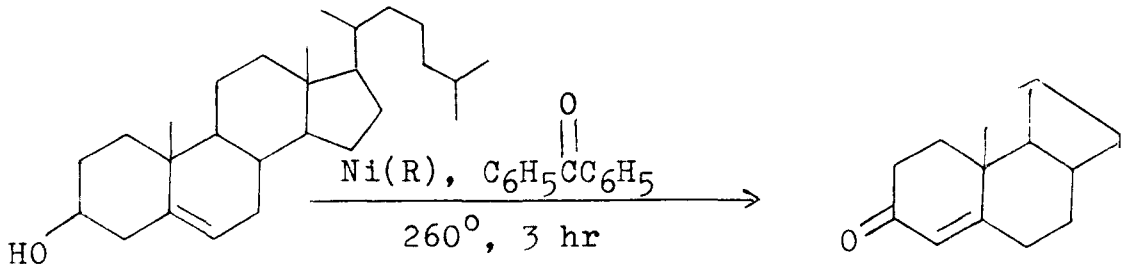
(I) (LIV)

2-Nitro-$\triangle^2$-cholestene (LV) when subjected to Zn/AcOH reduction, furnished cholestan-2-one (LVI)[17].

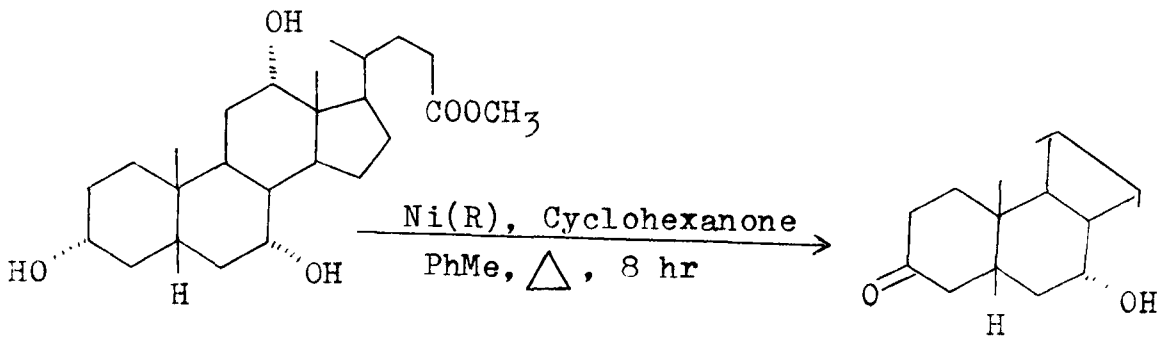


(LV) (LVI)

Raney nickel was used for the dehydrogenation of sterols by Foster et al.[18]. When cholesterol (LVII) was treated at 260° for 3 hours with Raney nickel and benzophenone gave cholest-4-en-3-one (LVIII) Similarly trihydroxy compound (LIX) gave 3-ketone (LX) when treated with Raney nickel and cyclohexanone in toluene.

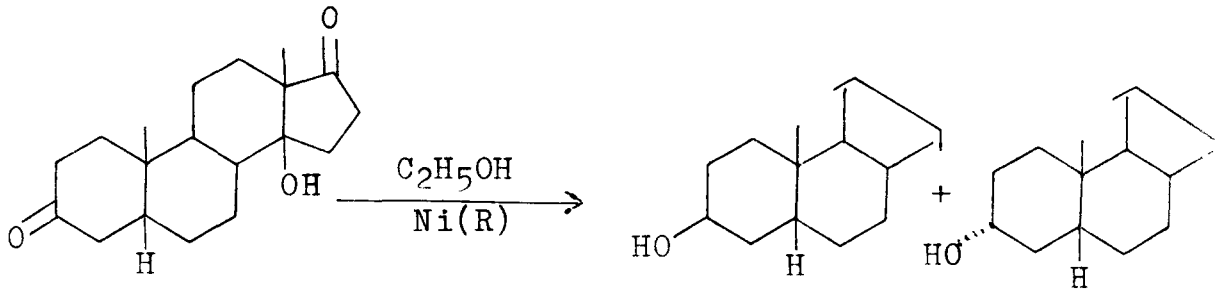


(LVII) (LVIII)



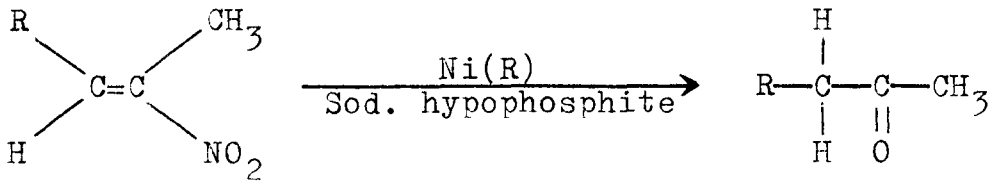
(LIX) (LX)

Reduction of 14β-hydroxy-5β,14β-estran-3,17-dione (LXI) in 95% aqueous ethanol containing Raney nickel gave 3β,14β-dihydroxy-5β,14β-estran-17-one (LXIIa) and 3α,14β-dihydroxy-5β,14β-estran-17-one (LXIIb)[19].

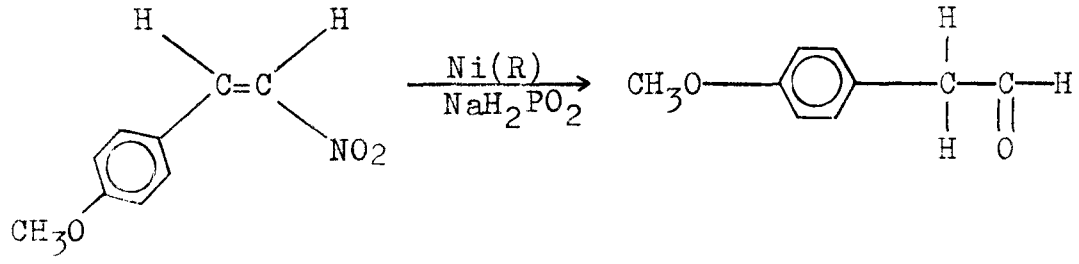


(LXI) (LXIIa) (LXIIb)

Monti et al.[20] have reported a mild method for converting nitroolefin into ketone or aldehyde using Raney nickel. Thus when compound (LXIII) was treated with Raney nickel and aqueous sodium hypophosphite in aqueous ethanol (pH 5) at 40-60° for 2 hours gave (LXIV) in 56-92% yield. Similar reaction of (LXV) gave 53% of (LXVa).

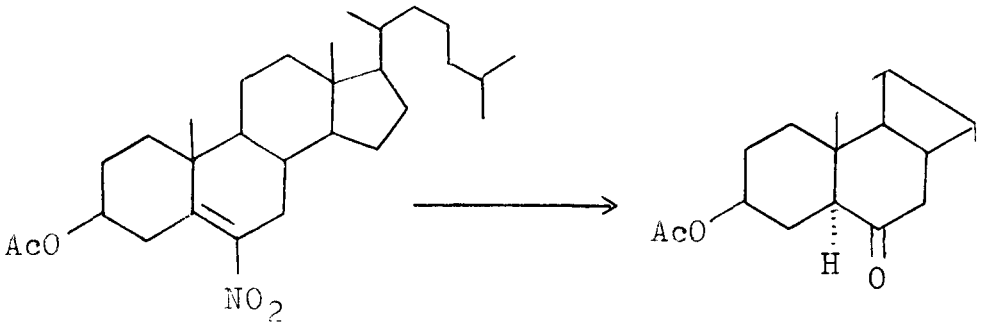


(LXIII) (LXIV)



(LXV) (LXVI)

It has been shown[20] that 3β-acetoxy-6-nitrocholest-5-ene (I) under the same reaction conditions provided 3β-acetoxy-5α-cholest-6-one (LXVII). Mention has also been made that under the same conditions nitroparaffins are reduced to amines while oximes give the corresponding carbonyl compounds in almost quantitative yields.



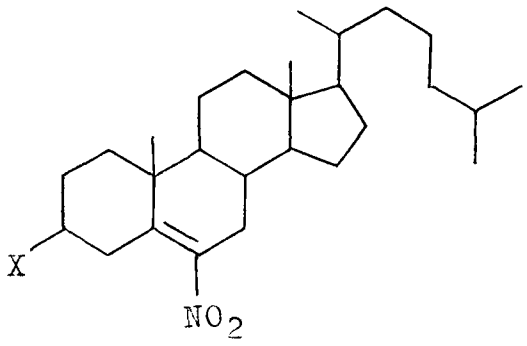
(I) (XLVI)

Wisniak and Klein[21] have shown the reduction of nitrobenzene to aniline using Raney nickel as catalyst. It has also been mentioned that the catalysis proceeds via PhNO:NPh and PhN:NPh intermediates.

Discussion

Reduction is a very common phenomenon in synthetic organic chemistry. The most commonly used reducing agents are the metal hydrides and hydrogen (with a catalyst)[22]. These are very powerful, but unselective in nature. More importance has always been given towards the selectivity rather than the reactivity of the reagent, for developing the useful and uniform synthetic routes. Subsequently a number of reagents have been endeavoured. A good amount of work has been carried out in this connection and a variety of reagnets have been prepared by replacing the hydrogen of $LiAlH_4$ with alkoxy groups[23]. Sodium borohydride ($NaBH_4$) was employed to a large extent in reducing the steroidal ketones[24]. The stereoselective nature of metal-ammonia was revealed when it was employed in the reduction of steroidal enones, saturated ketones and ketols[24].

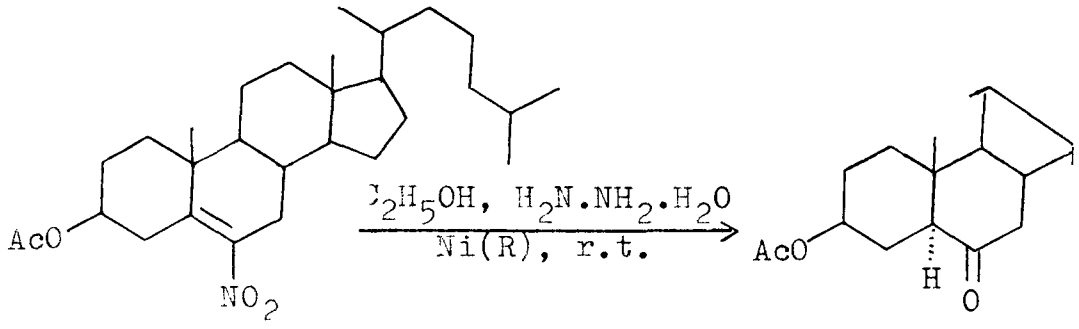
Limited findings were seen in the literature on Raney nickel catalysed reduction and no work has been carried out with steroidal nitro compounds. We considered it expedient to study the reducing action on steroidal nitro compounds. In this connection 3β-acetoxy-6-nitrocholest-5-ene (I), 6-nitrocholest-5-ene (XIX) and 3β-chloro-6-nitrocholest-5-ene (XXVII) were subjected to Raney nickel-hydrazine hydrate reduction.



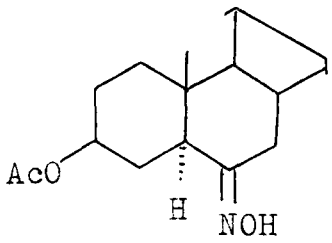
	X
(I)	OAc
(XXIX)	H
(XXVII)	Cl

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (I) with hydrazine hydrate-Raney nickel

3β-Acetoxy-6-nitrocholest-5-ene (I) in ethanol was treated with hydrazine hydrate in the presence of Raney nickel (as per the procedure of Furst and Moore)[25] at room temperature. After usual workup and subsequent column chromatography over silica gel, three crystalline products m.p. 128°, 202° and 144° were obtained.

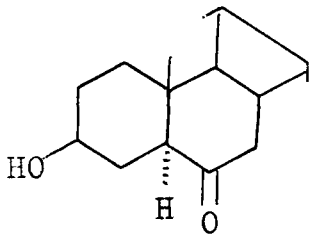


(I) (XLVI)



(XV)

+



(LXVI)

Characterization of the compound m.p. 128° as 3β-acetoxy-5α-cholestan-6-one (XLVI)

The compound (XLVI) m.p. 128° (reported[27] m.p. 127°) was analysed for $C_{29}H_{48}O_3$. In the IR spectrum bands were found at 1720 and 1235 cm^{-1} (acetoxy group). A broad multiplet centered at δ 4.58 in its NMR spectrum was assigned to C3-α proton ($W_{\frac{1}{2}}$ = 15Hz)[26]. A sharp singlet at δ 2.05 was for acetoxy protons. The methyl protons appeared at δ 1.13, 0.91, 0.79 and 0.63. These data confirmed that the compound is 3β-acetoxy-5α-cholestan-6-one (XLVI) which was identical with its authentic sample (t.l.c., m.p., m.m.p., i.r. and n.m.r.)[27].

Characterization of the compound m.p. 202° as 3β-acetoxy-5α-cholestan-6-one oxime (XV)

The compound m.p. 202° (reported[28] m.p. 201-202°) was analysed for $C_{29}H_{49}NO_3$. The bands at 3260 (N-OH), 1720 and 1240 cm^{-1} (CH_3COO) were observed in its IR spectrum. Signals at δ 9.1 (N-OH, exchangeable with D_2O) and at 2.0 (acetate protons) were seen. The C3-α<u>H</u> appeared as a multiplet at δ 4.93

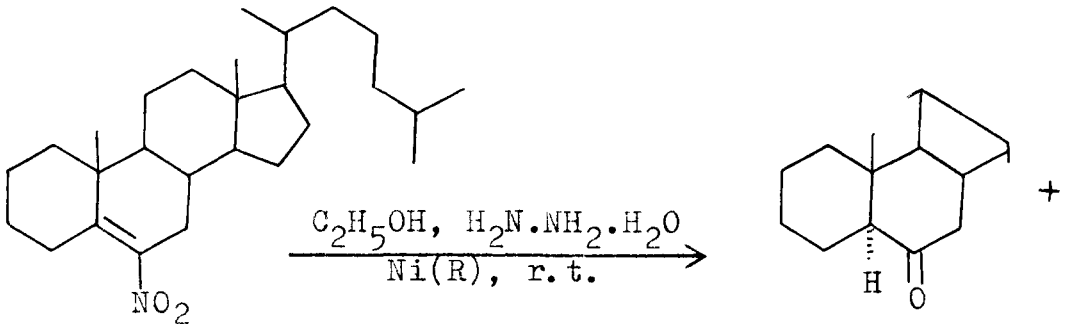
($W_{\frac{1}{2}}$ = 15Hz). Methyl protons appeared at δ 1.16, 0.9, 0.78 and 0.65. The spectral data suggested that the compound is 3β-acetoxy-5α-cholestan-6-one oxime (XV), (identical, t.l.c., m.p., m.m.p., i.r. and n.m.r. with authentic sample)[28].

Characterization of compound m.p. 144° as 3β-hydroxy-5α-cholestan-6-one (LXVI)

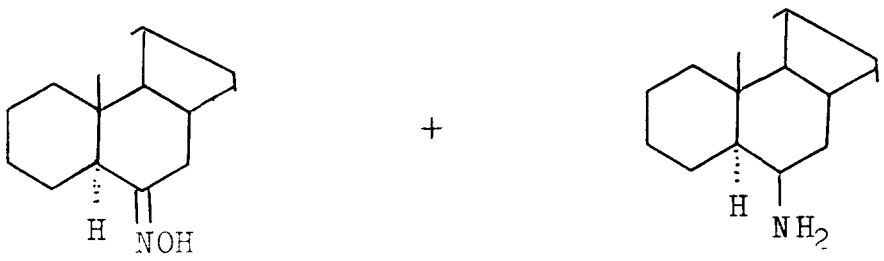
The compound (LXVI) m.p. 144° (reported[29] m.p. 142-143°) was analysed for $C_{27}H_{46}O_2$. A broad band in its IR spectrum at 3460 (-OH) and a sharp band at 1705 cm^{-1} (C=O) were exhibited. In its NMR spectrum a multiplet centred at δ 3.38 was observed for C3-αH ($W_{\frac{1}{2}}$ = 18Hz) and no signal appeared for acetoxy protons. Methyl protons gave peaks at δ 1.13, 0.91, 0.82 and 0.67. After comparison (t.l.c., m.p., m.m.p., i.r. and n.m.r.) with authentic sample[29] the compound (LXVI) was confirmed as 3β-hydroxy-5α-cholestan-6-one.

Reaction of 6-nitrocholest-5-ene (XXIX) with hydrazine hydrate-Raney nickel

The reaction of 6-nitrocholest-5-ene (XXIX) in ethanol with hydrazine hydrate-Raney nickel at room temperature afforded three compounds m.p. 97°, 202° and 187°.



(XXIX) (XLIX)



(LXVII) (LXVIII)

Characterization of compound m.p. 97° as 5α-cholestan-6-one(XLIX)

The compound (XLIX) m.p. 97° (reported[30] m.p. 95-96°) had analysis $C_{27}H_{46}O$. Its IR spectrum gave band at 1700 cm^{-1} (C=O). The NMR spectrum was featureless. The compound was found identical (t.l.c., m.p., m.m.p. and i.r.) with authentic sample of 5α-cholestan-6-one (XLIX)[30].

Characterization of compound m.p. 202° as 5α-cholestan-6-one oxime (LXVII)

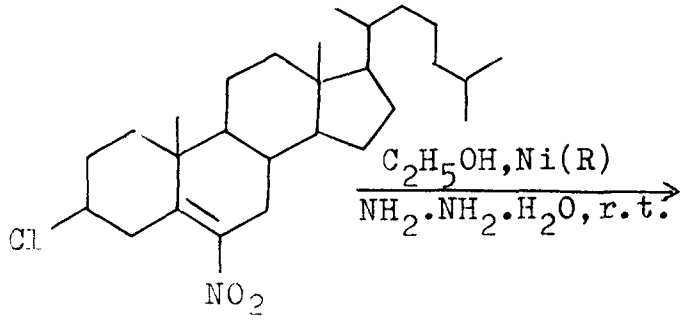
The compound (LXVII) m.p. 202° (reported[31] m.p. 204°) was analysed for $C_{27}H_{47}NO$. Its IR spectrum showed bands at 3240 (N-OH) and 1660 cm^{-1} (C=N). In its NMR spectrum a peak was observed at δ 9.7 (N-OH; exchangeable with D_2O). A double doublet due to C5-α<u>H</u> was observed at δ 3.44 (J_{aa} 10Hz; J_{ae} 5Hz). Angular and other methyl proton signals were seen at δ 1.10, 0.93, 0.83 and 0.68. The compound was identical (t.l.c., m.p., m.m.p., i.r. and n.m.r.) with 5α-cholestan-6-one oxime (LXVII)[31].

Characterization of compound m.p. 187° as 6β-amino-5α-cholestane (LXVIII)

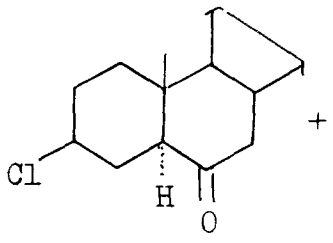
The compound (LXVIII) m.p. 187° showed molecular composition $C_{27}H_{49}N$ which indicated that oxygen is not present. In the IR spectrum band at 3200 cm^{-1} ($-NH_2$) was observed. A multiplet centred at δ 3.20 in its NMR spectrum was assigned to C6-α proton ($W_{\frac{1}{2}}$ = 12Hz; equatorial). The signal for $-NH_2$ protons was observed at δ 1.50[32] as a broad peak ($W_{\frac{1}{2}}$ = 9Hz). The methyl protons appeared at δ 1.20 (C10-C<u>H</u>$_3$), 0.66 (C13-C<u>H</u>$_3$), 0.93 and 0.83 (remaining methyl protons). From these observations the compound (LXVIII) was regarded as 6β-amino-5α-cholestane. It is worth mentioning here that the formation of amine is in accordance with the results of Furst and Moore[25].

Reaction of 3β-chloro-6-nitrocholest-5-ene (XXVII) with hydrazine hydrate-Raney nickel

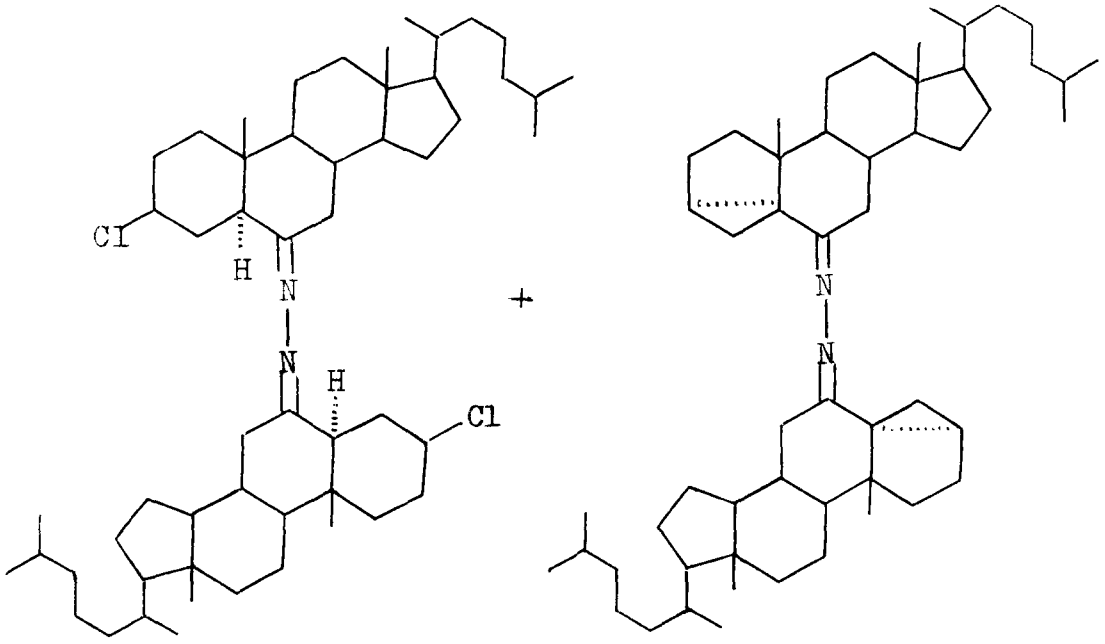
3β-Chloro-6-nitrocholest-5-ene (XXVII) was treated with hydrazine hydrate-Raney nickel at room temperature and three crystalline compounds m.p. 129°, 171° and 207° were obtained.



(XXVII)



(XLVII)



(LXIX) (LXX)

Characterization of compound m.p. 129° as 3β-chloro-5α-cholestan-6-one (XLVII)

The compound (XLVII) m.p. 129° (reported[33] m.p. 129-130°) was analysed for $C_{27}H_{45}OCl$ (positive Beilstein test). For this compound there were bands at 1700 (C=O) and 750 cm^{-1} (C-Cl) in the IR spectrum. A broad multiplet at δ 3.7 ($W_{\frac{1}{2}}$ = 18Hz) ascribable to C3-α<u>H</u> (axial) was seen. Peaks at δ 1.2, 0.9, 0.81 and 0.7 were also observed (methyl protons). The compound was found identical (t.l.c., m.p., m.m.p., i.r. and n.m.r) with 3β-chloro-5α-cholestan-6-one (XLVII)[33].

Characterization of the compound, m.p. 171° as 3β,3'β-dichloro-5α,5'α-6,6'-bis azocholestane (LXIX)

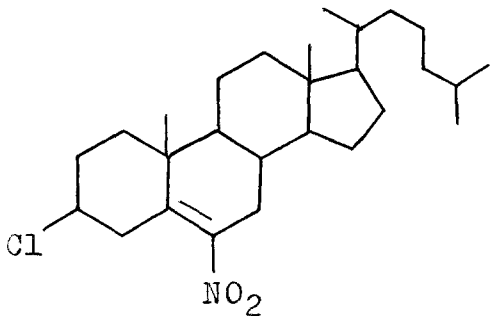
The compound (LXIX) m.p. 171° was analysed for $C_{54}H_{90}N_2Cl_2$ and gave molecular ion peaks at M^+ 834/836/838. The bands at 1625 (C6=N-N=C'6) and at 720 cm^{-1} (C3-Cl and C'3-Cl) were exhibited in the IR spectrum. In its NMR spectrum a multiplet centered at δ 3.7 appeared which was ascribed to C3-α and C'3-α protons ($W_{\frac{1}{2}}$ = 17Hz; axial)[26]. The methyl protons appeared at δ 1.2 (C10-C<u>H</u>$_3$ and C'10-C<u>H</u>$_3$). 0.70 (C13-C<u>H</u>$_3$ and C'13-C<u>H</u>$_3$), 0.91 and 0.83 (remaining methyl protons). From the above data it may be suggested that the compound m.p. 171° is 3β,3'β-dichloro-5α,5'α-6,6'-bis azocholestane (LXIX).

Characterization of the compound m.p. 207° as 3α,5α-3'α,5'α-cyclo-6,6'-bisazocholestane (LXX)

The compound m.p. 207° (LXX) was analysed for $C_{54}H_{88}N_2$. The molecular ion peak M^+ 764 supported the molecular composition. Its IR spectrum exhibited bands at 3030 (cyclopropane rings system -C-C-) and 1625 cm^{-1} (C6=N-N=C'6). The NMR spectrum was featureless except for the characteristic complex signal at δ 0.5-0.65 for the cyclopropane rings protons. The methyl protons appeared at δ 1.18 (C10-C$\underline{H}_3$ and C'10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$ and C'13-C$\underline{H}_3$), 0.93 and 0.83 (remaining methyl protons). From the molecular composition, molecular ion peak and the other spectral data it may be suggested that the compound is 3α,5α-3'α,5'α-cyclo-6,6'-bisazocholestane (LXX).

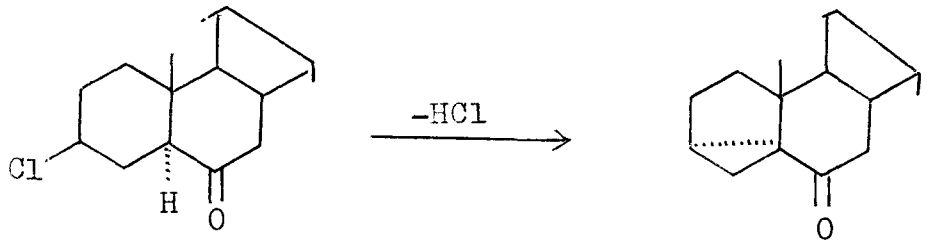
Monti et al.[20] have shown that, the reaction of nitroolefins with Raney nickel and sodium hypophosphite gave exclusively carbonyl compounds and nitroparaffins were reduced to amines. But in our case the reaction with hydrazine hydrate-Raney nickel provided oximes, diazo compounds and amine along with the usual reduction product, the carbonyl compounds. This suggests that by controlling the reaction parameters, the desired products could be obtained. In this way hydrazine hydrate-Raney nickel reduction could be made into a selective one.

It may be suggested that the nitroolefin (XXVII) which was reduced to the corresponding ketone (XLVII) inturn gave 3α,5 - cyclo-5α-cholestan-6-one (XLVIIa) during the course of the reaction, which ofcourse was not isolated. The two ketones (XLVII and XLVIIa) thus formed reacted with hydrazine hydrate to give the dimeric diazo compounds (LXIX) and (LXX). A tentative mechanism may be proposed to explain the formation of the dimers.

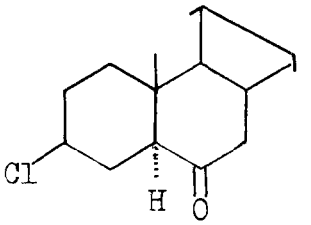


(XXVII)

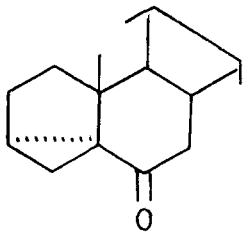
$C_2H_5OH/H_2N.NH_2.H_2O/Ni(R)$, r.t.



(XLVII) (XLVIIa)

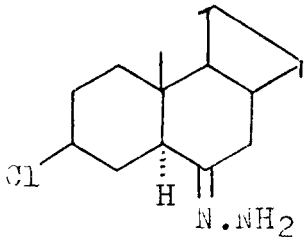


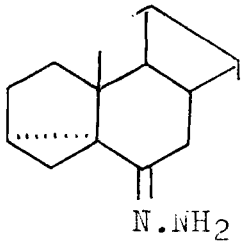
(XLVII)

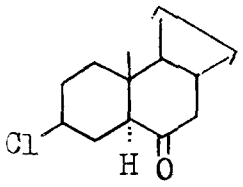


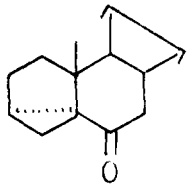
(XLVIIa)

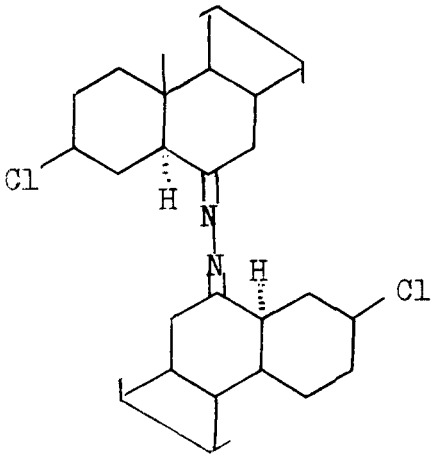
$NH_2.NH_2$

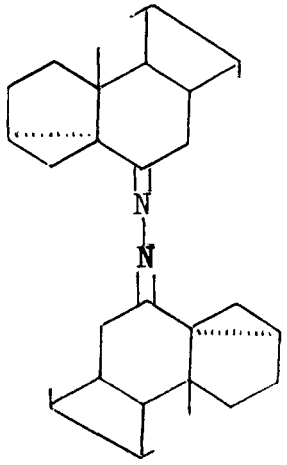












(LXIX)

(LXX)

Experimental

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (I) with hydrazine hydrate-Raney nickel: 3β-Acetoxy-5α-cholestan-6-one (XXI), 3β-acetoxy-5α-cholestan-6-one oxime (XV) and 3β-hydroxy-5α-cholestan-6-one (LXVI)

To a solution of 3β-acetoxy-6-nitrocholest-5-ene (I) (3 g) in ethanol (100 ml) was added hydrazine hydrate (5 ml; 100%). Raney nickel (0.75 g) was added in small portions and the temperature of the reaction mixture was maintained below 30°. It was kept at room temperature for 2-3 hours. On completion of the reaction (checked by running TLC at frequent interval) the mixture was filtered and the filtrate was diluted with water, and extracted with ether. The ethereal layer was washed with water, sodium hydrogen carbonate solution (5%) and water. Dried over anhydrous sodium sulphate. Evaporation of the solvent provided an oily residue which was chromatographed over a column of silica gel (60 g). Elution with light petroleum ether:ether(20:1) furnished 3β-acetoxy-5α-cholestan-6-one (XXI), recrystallized from methanol (400 mg), m.p. 128° (reported[27] m.p. 127°).

Analysis Found : C, 78.31; H, 10.84

$C_{29}H_{48}O_3$ requires : C, 78.37; H, 10.81%

IR : $\nu_{max.}$ 1720 and 1235 cm^{-1} (C=O and C-O of acetoxy group).

NMR : δ 4.58 br,m(C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 15 Hz), 2.05 s($C\underline{H}_3$-COO), 1.13 (C10-$C\underline{H}_3$), 0.63 (C13-$C\underline{H}_3$), 0.91 and 0.79 (other methyl protons).

Further elution with light petroleum ether:ether (15:1) provided 3β-acetoxy-5α-cholestan-6-one oxime (XV), recrystallized from ethanol (600 mg), m.p. 202° (reported[28] m.p. 201-202°).

Analysis Found : C, 75.85; H, 10.64; N, 3.12

$C_{29}H_{49}NO_3$ requires : C, 75.81; H, 10.67; N, 3.05%

IR : $\nu_{max.}$ 3260 (N-OH), 1720 and 1240 cm^{-1} (CH_3COO)

NMR : δ 9.1 (NOH, exchangeable with D_2O), 4.93 m(C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 15Hz), 2.00 s($C\underline{H}_3COO$), 1.16 (C10-$C\underline{H}_3$), 0.65(C13-$C\underline{H}_3$, 0.9 and 0.78 (remaining methyl protons).

Continued elution with light petroleum ether:ether (10:1) gave 3β-hydroxy-5α-cholestan-6-one (LXVI) recrystallized from methanol (300 mg), m.p. 144° (reported[29] m.p. 142-143°).

Analysis Found : C, 80.64; H, 11.40

$C_{27}H_{46}O_2$ requires : C, 80.59; H, 11.44%

IR : $\nu_{max.}$ 3460 (OH) and 1705 cm^{-1} (C=O).

NMR : δ 3.38 m(C3-α$\underline{H}$; axial, $W_{\frac{1}{2}}$ = 18Hz), 1.20 (C10-$C\underline{H}_3$), 0.69 (C13-$C\underline{H}_3$), 0.90 and 0.81 (remaining methyl protons).

<u>Reaction of 6-nitrocholest-5-ene (XXIX) with hydrazine hydrate-Raney nickel:5α-Cholestan-6-one (XLIX), 5α-cholestan-6-one oxime (LXVII) and 6β-amino-5α-cholestane (LXVIII)</u>

6-Nitrocholest-5-ene (XXIX) (3 g) was treated with hydrazine hydrate (5 ml; 100%)-Raney nickel (0.75 g) as in the previous case. Work up of the reaction mixture followed by evaporation of the

solvent yielded a brown residue which was chromatographed over silica gel (60 g). Elution with petroleum ether:ether (20:1) provided 5α-cholestan-6-one (XLIX), recrystallized from ethanol (100 mg) m.p. 97° (reported[30] m.p. 95-96°)

Analysis Found : C, 83.9; H, 11.87

$C_{27}H_{46}O$ requires : C, 83.93; H, 11.91%

IR : $\nu_{max.}$ 1700 cm^{-1} (C=O).

Further elution with petroleum ether:ether (15:1) yielded 5α-cholestan-6-one oxime (LXVII) recrystallized from ethanol (700 mg) m.p. 202° (reported[31] m.p. 204°).

Analysis Found : C, 81.44; H, 11.37; N, 3.54

$C_{27}H_{47}NO$ requires : C, 81.40; H, 11.31; N, 3.59%

IR : $\nu_{max.}$ 3240 (-NOH), 1660 cm^{-1} (C=N)

NMR : δ 9.7 (=NO<u>H</u>; exchangeable with deuterium), 3.44 dd (J = 10Hz and 5Hz; C5-α<u>H</u>; axial), 1.10(C10-C<u>H</u>$_3$), 0.68 (C13-C<u>H</u>$_3$), 0.93 and 0.83 (remaining methyl protons).

Continued elution with petroleum ether:ether (12:1) gave 6β-amino-5α-cholestane(LXVIII), recrystallized from ethanol (500 mg), m.p. 187°.

Analysis Found : C, 83.77; H, 12.63; N, 3.65

$C_{27}H_{49}N$ requires : C, 83.72; H, 12.66; N, 3.61%

IR : $\nu_{max.}$ 3200 cm^{-1} (-NH_2)

NMR : δ 3.20 mc (C6-α<u>H</u>), 1.5 br,s(-NH_2), 1.20 (C10-C<u>H</u>$_3$), 0.66 (C13-C<u>H</u>$_3$), 0.93 and 0.83 (remaining methyl protons).

Reaction of 3β-chloro-6-nitrocholest-5-ene (XXVII) with hydrazine hydrate-Raney nickel: 3β-Chloro-5α-cholestan-6-one (XLVII), 3β,3'α-dichloro-5α,5'α-6,6'-bisazocholestane (LXIX) and 3α,5α-3'α,5'α-cyclo-6,6'-bisazocholestane (LXX)

3β-Chloro-6-nitrocholest-5-ene (XXVII) (3 g) in ethanol (100 ml) was treated with hydrazine hydrate (5 ml; 100/) in the presence of Raney nickel (0.75 g) at ambient temperature as in the previous case. After the completion of the reaction, the reaction mixture was filtered, the filtrate was diluted with water and extracted with ether. The ethereal layer was washed with water, sodium hydrogen carbonate solution (5%) and water. The extract was dried over anhydrous sodium sulphate and evaporation of the solvent provided a residue which was chromatographed over a column of silica gel. Elution with petroleum ether:ether (20:1) afforded 3β-chloro-5α-cholestan-6-one (XLVII), recrystallized from methanol (100 mg), m.p. 129° (reported[32] m.p.129-130°).

Analysis Found : C, 77.17; H, 10.74

$C_{27}H_{45}OCl$ requires : C, 77.14; H, 10.71%

IR : $\nu_{max.}$ 1700 (C=O) and 750 cm^{-1} (C-Cl).

NMR : δ 3.7 (C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 18Hz), 1.2 (C10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$), 0.9 and 0.81 (remaining methyl protons).

Further elution with petroleum ether:ether (15:1) gave an oil (LXIX) crystallized from methanol (900 mg), m.p. 171°.

Analysis Found : C, 77.58; H, 10.71; N, 3.37

$C_{54}H_{90}N_2Cl_2$(M^+ 834/836/838) requires : C, 77.51, H, 10.76; N, 3.34%

IR : $\gamma_{max.}$ 1625 (C6=N-N=C'6) and 720 cm^{-1} (C3-Cl and C'3-Cl)

NMR : δ 3.7 m(C3-α$\underline{H}$ and C'3-α$\underline{H}$; W½ = 17 Hz), 1.2 (C10-C$\underline{H}_3$ and C'10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$ and C'13-C$\underline{H}_3$), 0.83 and 0.91 (remaining methyl protons).

Continued elution with light petroleum ether:ether (13:1) provided the compound (LXX) recrystallized from methanol (700 mg), m.p. 207°.

Analysis Found : C, 84.87; H, 11.46; N, 3.61

$C_{54}H_{88}N_2$(M^+ 764) requires : C, 84.81; H, 11.51; N, 3.66%

IR : $\gamma_{max.}$ 3030 (-C$\overset{\diagup\diagdown}{\underset{\diagdown\diagup}{C}}$C-) and 1625 cm^{-1} (C6=N-N=C'6)

NMR : δ 0.5-0.65 complex signals (cyclopropnae rings protons), 1.18 (C10-C$\underline{H}_3$ and C'10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$ and C'13-C$\underline{H}_3$), 0.93 and 0.83 (remaining methyl protons).

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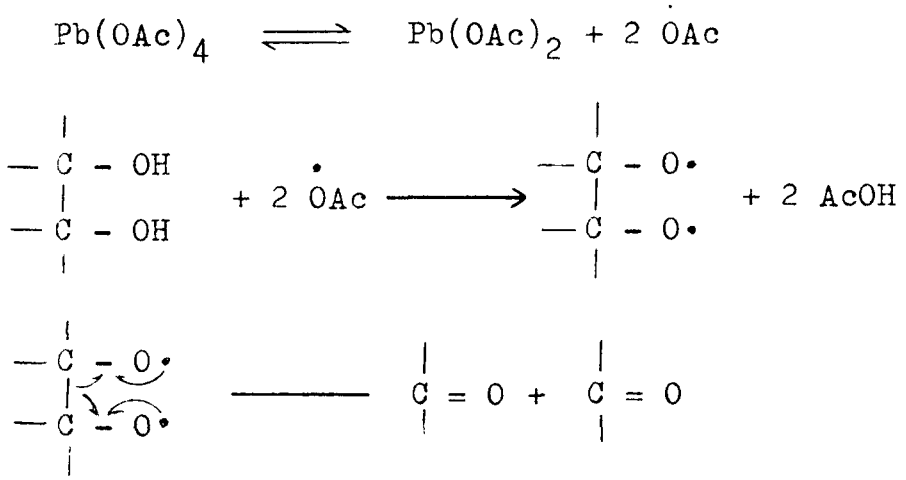
Part Four

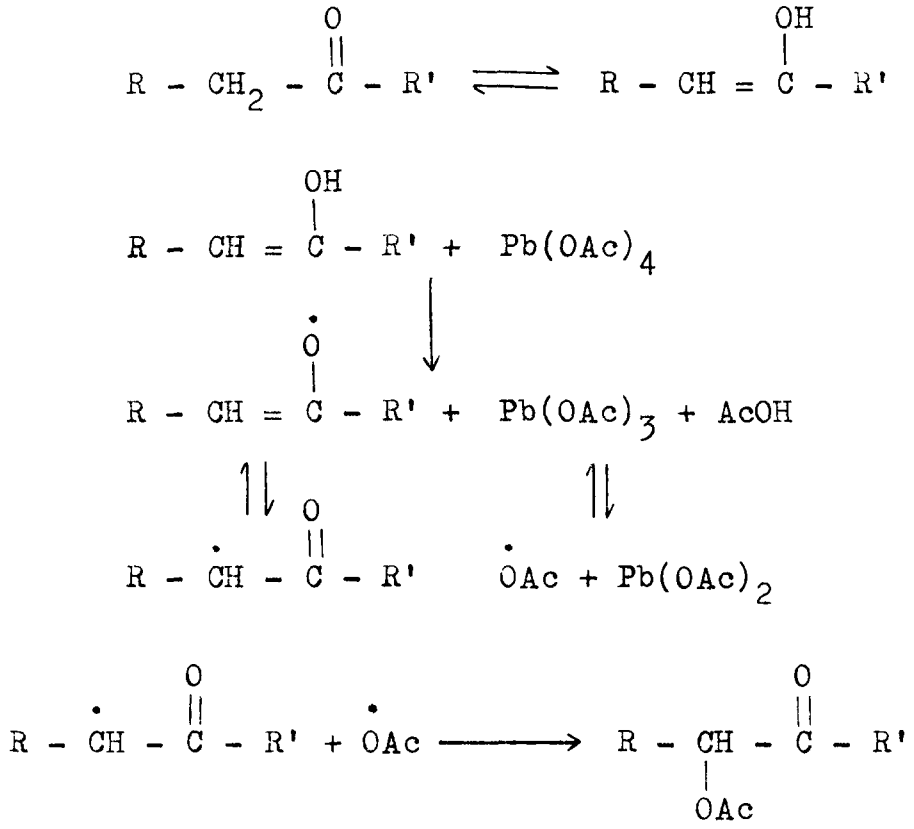
Oxidation of Steroidal 6-Nitroolefins With Lead Tetraacetate

Theoretical

Lead tetraacetate is one of the versatile reagents used in synthetic organic and inorganic chemistry. Mostly it is used as an oxidising agent and cases in which it is widely used as methylating and acetylating agent are also known[1-7]. It is known that it readily reacts with compounds containing -OH, -NHR, C=O, $-NH_2$ and -COOH groups on two adjacent carbon atoms. During oxidation by lead tetraacetate, C-C bond cleavage is an interesting feature[8]. Lead tetraacetate is found to be of varied utility in the field of steroids too. Lead tetraacetate reacted with 1,2-diols to give carbonyl compounds. The mechanism proposed by Criegee et al.[8] in which cyclic ester intermediate does involve was criticised by Waters[9] who proposed the following free radical mechanism.

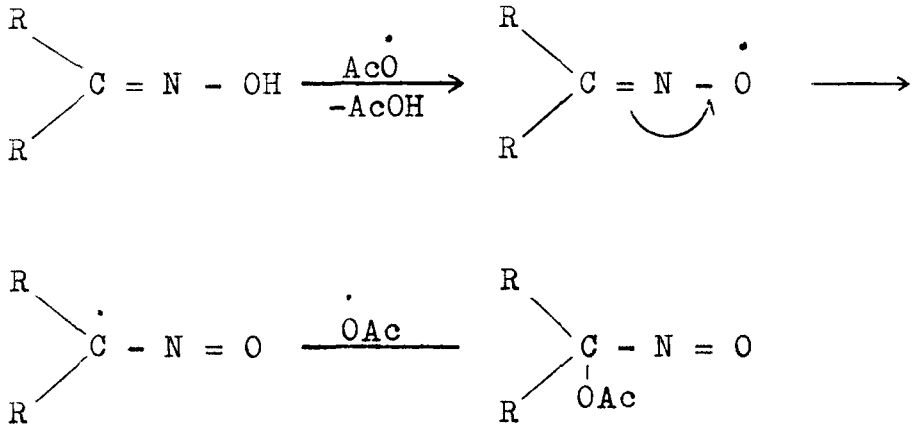


Cavill et al.[10] reported the α-acetoxylation of simple ketones and β-dicarbonyl systems by lead tetraacetate. The process involves a primary attack of lead tetraacetate on the enolic form of the carbonyl compound. The following free radical mechanism was proposed for the reaction of carbonyl compounds with lead tetraacetate.

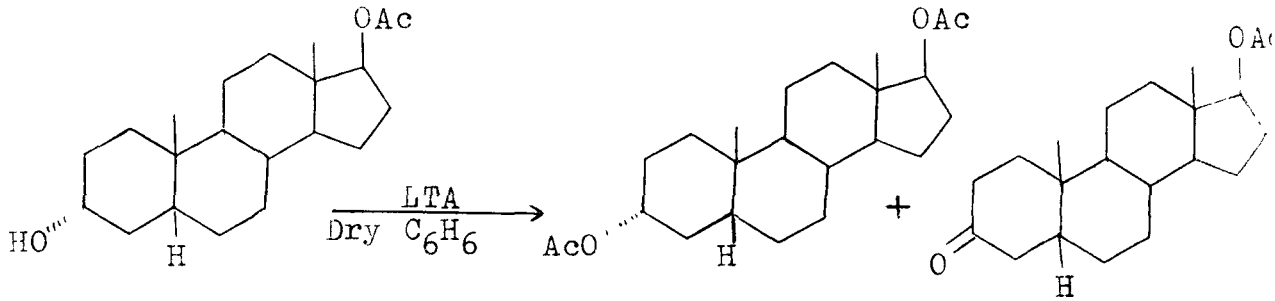


Formation of nitrosoacetate from oxime with lead tetra-acetate has been suggested to follow the pathway involving acetoxy free radical[11,12].

$$Pb(OAc)_4 \longrightarrow Pb(OAc)_2 + 2\ AcO^{\cdot}$$

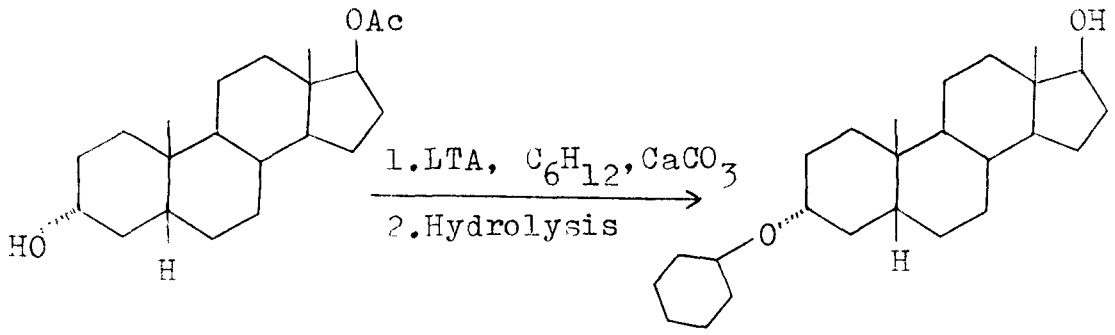


Some novel applications of lead tetraacetate on sex hormones have been reported by Immer et al.[13] 3α-Hydroxy-17β-acetoxy-5β-androstane (I) in dry benzene with lead tetraacetate afforded 3α,17β-diacetoxy-5β-androstane (II) and 3-oxo-17β-acetoxy-5β-androstane (III).

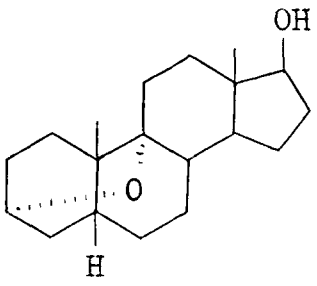


(I) (II) (III)

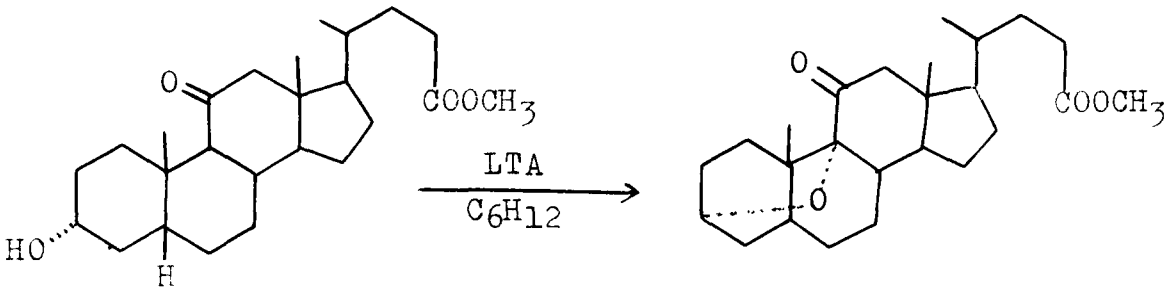
3α-Cyclohexyloxy-17β-hydroxy-5β-androstane (IV) and 3α,9-oxido-17β-hydroxy-5β-androstane (V) were obtained[13] when compound (I) was treated in cyclohexane with lead tetraacetate containing $CaCO_3$. Methyl-3α-hydroxy-11-oxo-5β-cholanate (VI) when treated with lead tetraacetate in cyclohexane yielded methyl-3α,9-oxido-11-oxo-5β-cholanate (VII)[13].



(I) (IV)

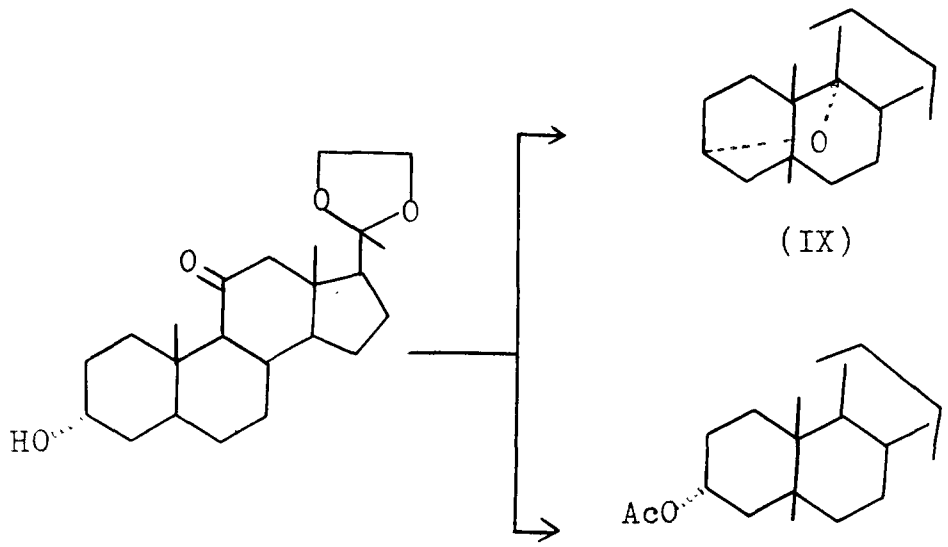


(V)



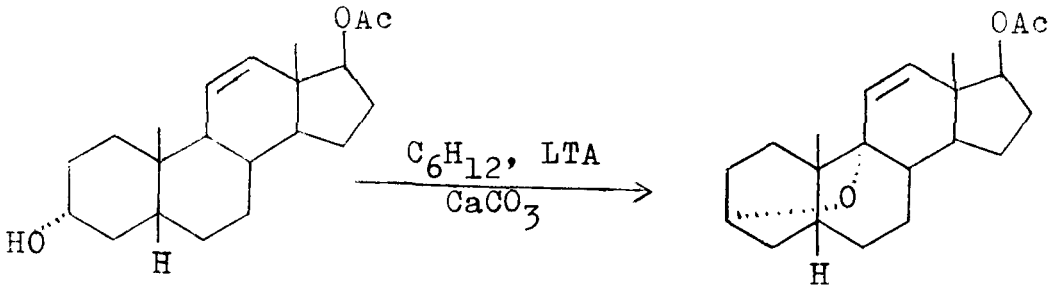
(VI) (VII)

5α-Hydroxy-11-oxo-20-ethylenedioxy-5β-pregnane (VIII) under similar conditions afforded 3α,9-oxido-11-oxo-20-ethylenedioxy-5β-pregnane (IX) and 3α-acetoxy-11-oxo-20-ethylenedioxy-5β-pregnane (X)[13].



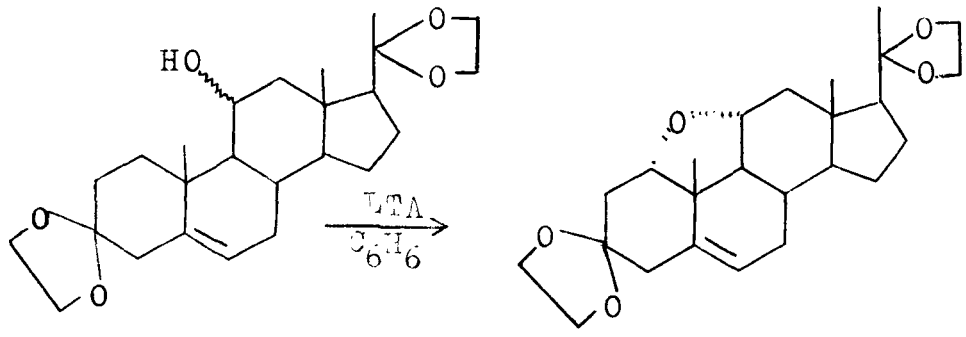
(VIII) (X)

Lead tetraacetate in the presence of $CaCO_3$ converted 3α-hydroxy-17β-acetoxy-5β-androst-11-ene (XI) into 3α-9-oxido-17β-acetoxy-5β-androst-11-ene (XII)[13].



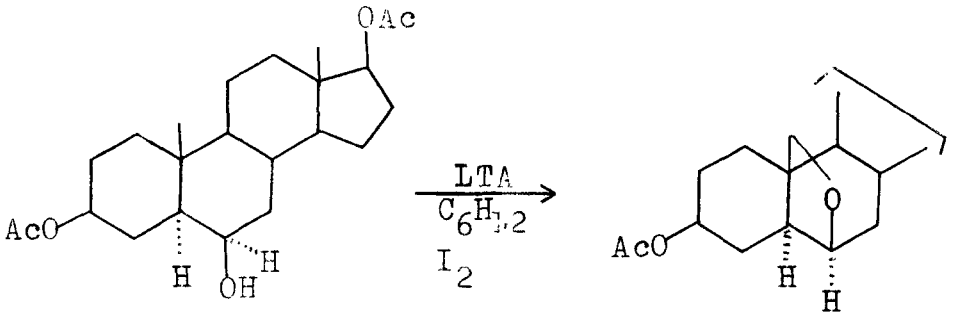
(XI) (XII)

Reaction of 3,20-bisethylenedioxy-11β-hydroxy-5-pregnene or its 11α-isomer (XIII) when reacted with lead tetraacetate in boiling benzene gave 1α,11α-epoxy-3,20-bisethylenedioxy-5 pregnene (XIV)[14].



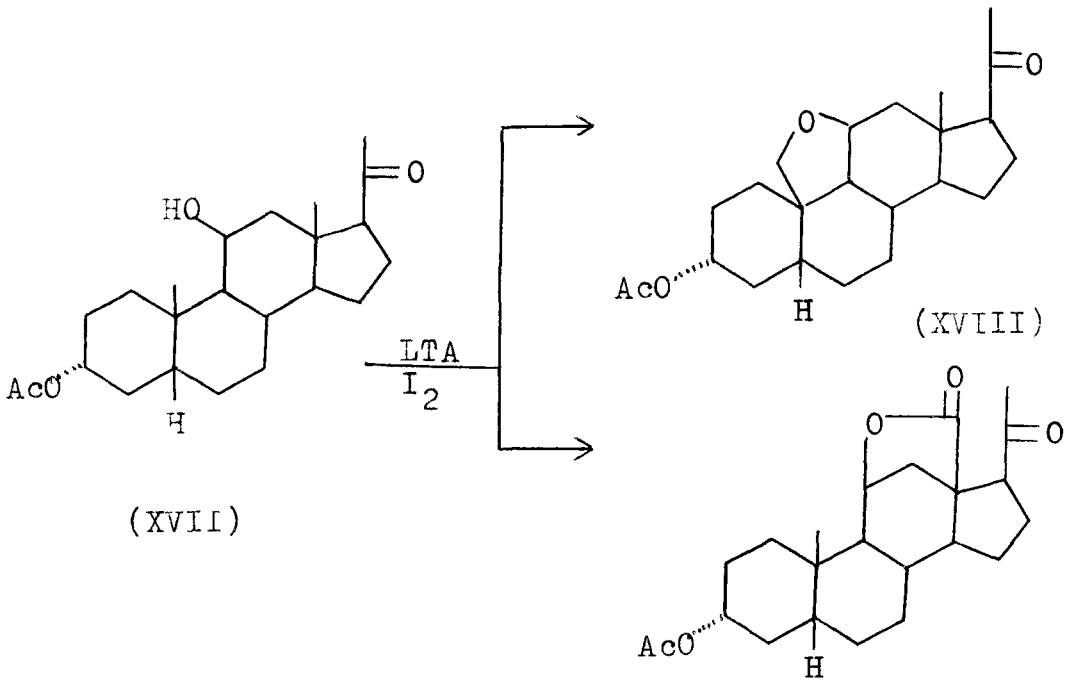
(XIII) (XIV)

Housler et al.[15] reported the isolation of 3β,17β-diacetoxy-6β,19-oxido-5α-androstane (XVI) when 3β,17β-diacetoxy-6β-hydroxy-5α-androstane (XV) reacted with lead tetraacetate in cyclohexane in the presence of iodine.



(XV) (XVI)

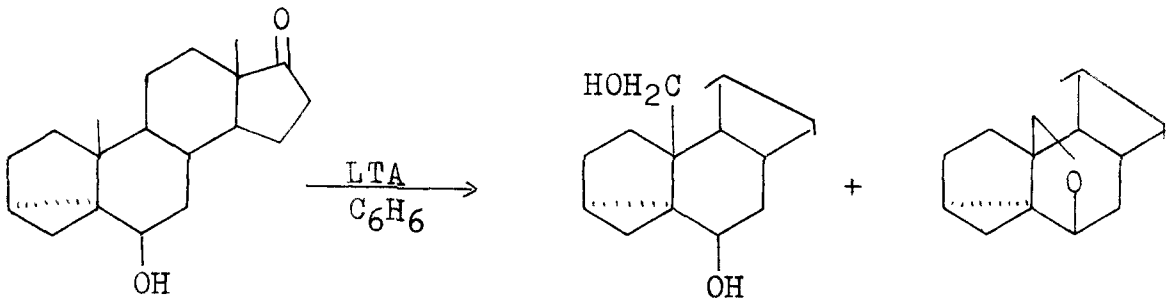
Meystre et al.[16] treated 5β-pregnane-3α,11β-diol-20-one-3-acetate (XVII) with excess of lead tetraacetate in the presence of iodine and isolated 5β-pregnane-3α-ol-11β,19β-oxido-20-one-3-acetate (XVIII) and 5β-pregnane-3α-ol-11β,18β-oxido-18,20-dione-3-acetate (XIX).



(XVII) (XVIII)

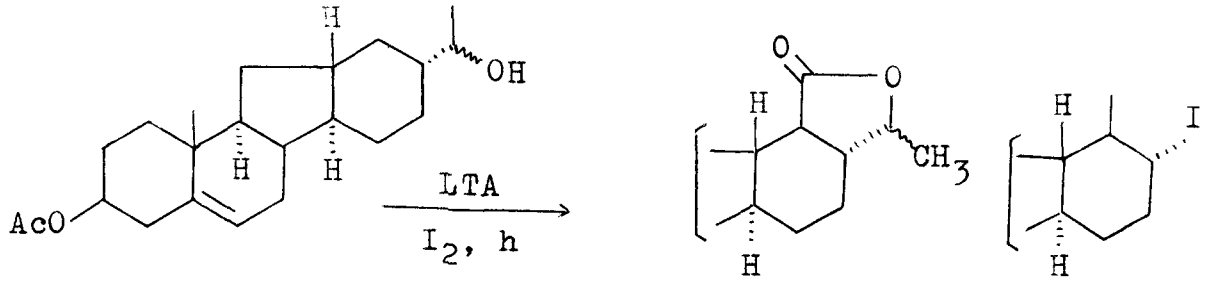
(XIX)

A solution of 6β-hydroxy-3α,5α-cycloandrostan-17-one (XX) in benzene with lead tetraacetate gave 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (XXI) and the expected 6β-19-oxido-3α,5α-cycloandrostan-17-one (XXII)[17].

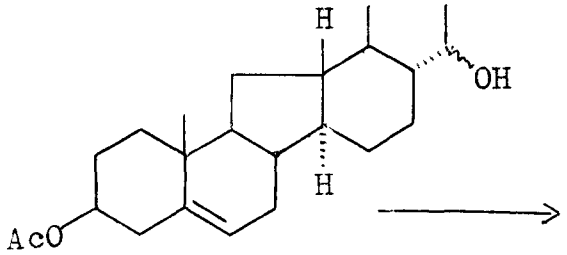


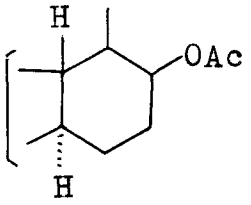
(XX) (XXI) (XXII)

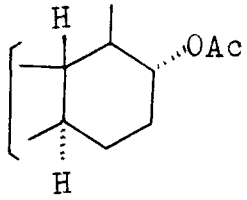
Irradiation of 3-O-acetyl-12β-etiojerv-5-ene-3β-20ξ-diol (XXIII) in benzene with lead tetraacetate in the presence of iodine provided (XXIV) and (XXV)[18]. Oxidation of (XXIII) with lead tetraacetate in benzene provided novel rearragned products (XXVI-XXX)[18].



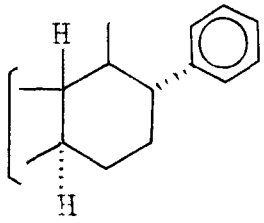
(XXIII) (XXIV) (XXV)

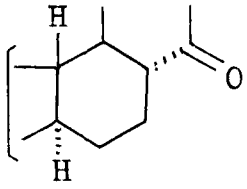


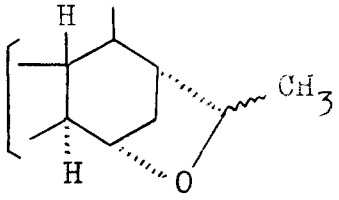




(XXIII) (XXVI) (XXVII)

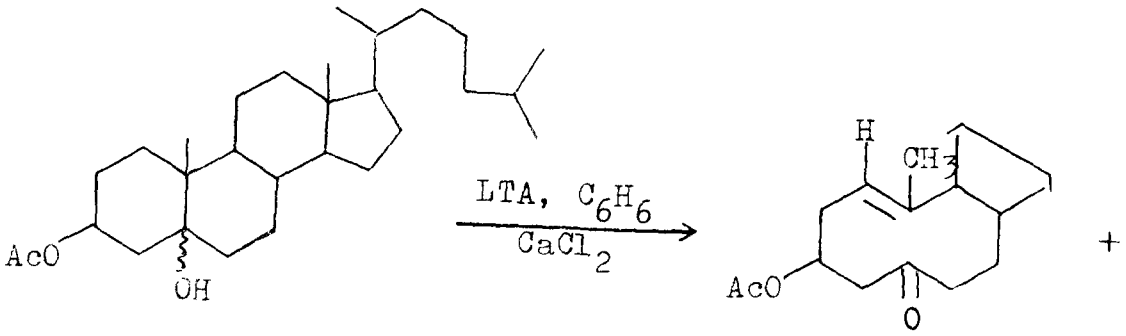






(XXVIII) (XXIX) (XXX)

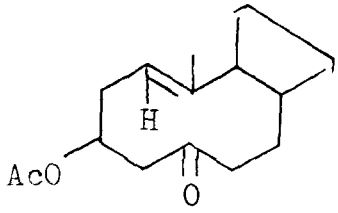
Lead tetraacetate oxidation of 5-hydroxysteroids provided 5,10-seco steroids[19]. Thus 3β-acetoxycholestan-5α-ol (XXXI) or its 5β-isomer (XXXII) when treated with one molar equivalent of lead tetraacetate in benzene afforded cis- and trans- 3β-acetoxy-5,10-seco-$\triangle^{1(10)}$-cholesten-5-ones (XXXIII and XXXIV).



(XXXI) α-OH

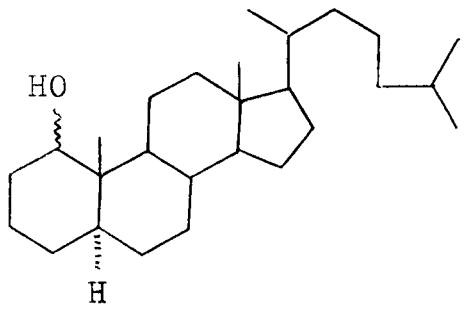
(XXXII) β-OH

(XXXIII)



(XXXIV)

Stefanovic et al.[20] reported that lead tetraacetate oxidation of cholestan-1-ol (XXXV) in benzene in the presence of $CaCO_3$ afforded products of ring cleavage, 10ξ-acetoxy-1,10-secocholestane-1-al (XXXVI) and 1,10-seco-$\Delta^{5,10(or\ 9,10)}$-cholesten-1-al (XXXVII) along with the normal products cholestane (XXXVIII), cholest-1-ene (XXXIX) and cholest-1-one (XL).

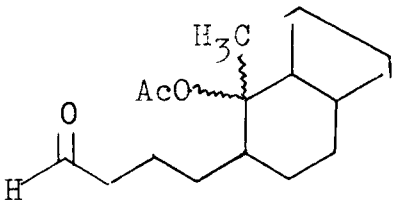


(XXXV)

$Pb(OAc)_4$

C_6H_6

$CaCO_3$



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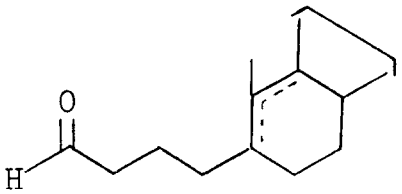
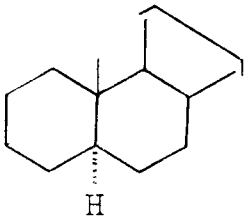


(XXXVI)

(XXXVII)



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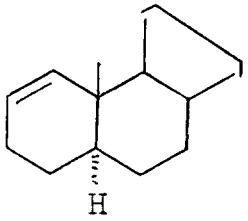

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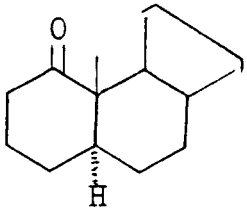
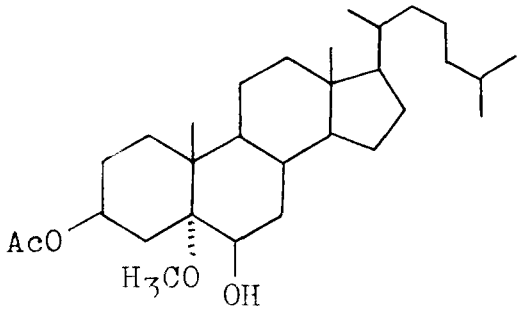


(XXXVIII)

(XXXIX)

(XL)

Morand and Kaufman[21] when performed the lead tetraacetate oxidation of 3β-acetoxy-5α-methoxycholestan-6β-ol (XLI), got 3β-acetoxy-5α-methoxycholestan-6-one(XLII), 3β-acetoxy-5α,6α-methylenedioxycholestane (XLIII) and 3β-acetoxy-5α-methoxy-6β, 19-oxidocholestane (XLIV). But a similar treatment of 3β-acetoxy-6β-methoxycholestan -5α-ol (XLV) gave 3β-acetoxy-5,6-seco-cholestan-5-on-6-al (XLVI) and 3β-acetoxy-B-nor-6ξ-formylcholestan-5ξ-ol (XLVII)[21].

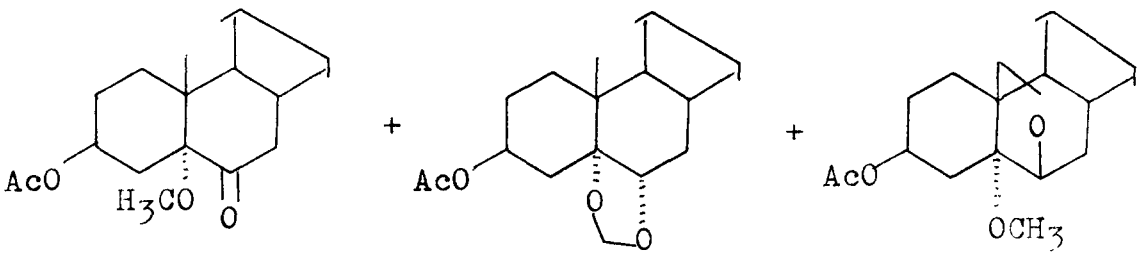


(XLI)

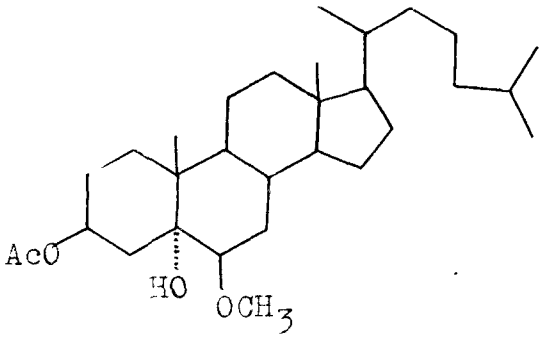
LTA

C_6H_6

$CaCO_3$

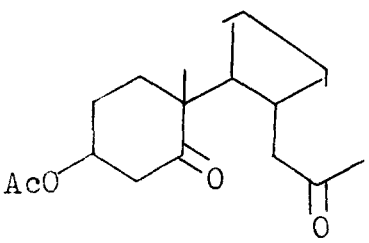


(XLII) (XLIII) (XLIV)



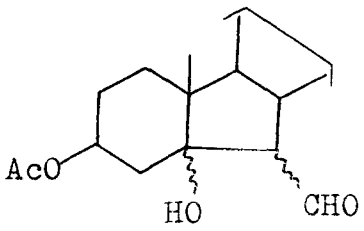
(XLV)

LTA
$CaCO_3$
C_6H_6



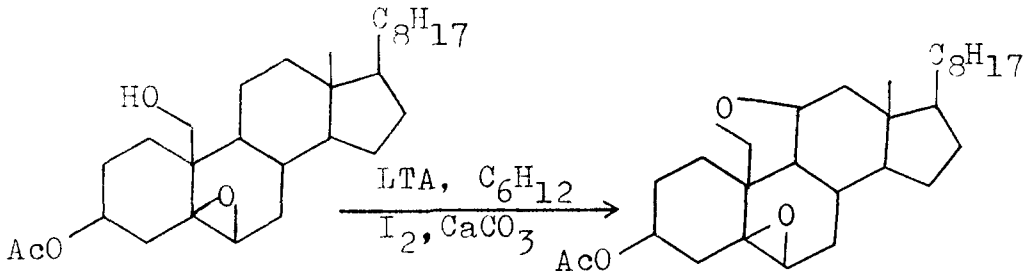
(XLVI)

+



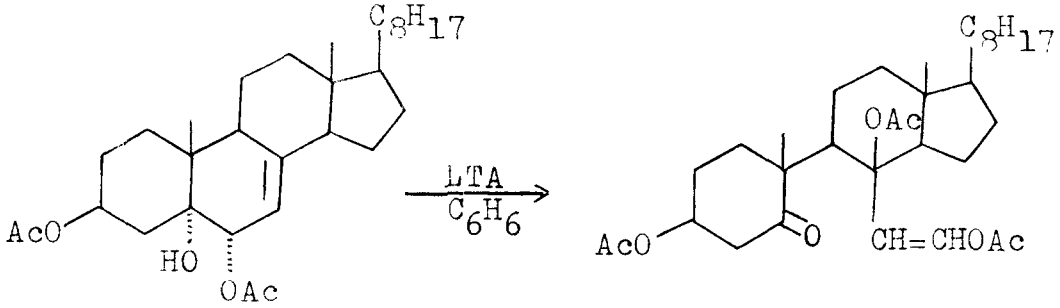
(XLVII)

3β-Acetoxy-5,6β-oxido-5β-cholestan-19-ol (XLVIII) on treatment with lead tetraacetate in cyclohexane in the presence of iodine and $CaCO_3$ provided 3β-acetoxy-5,6β:11β, 19-dioxido-5β-cholestane (XLIX)[22].

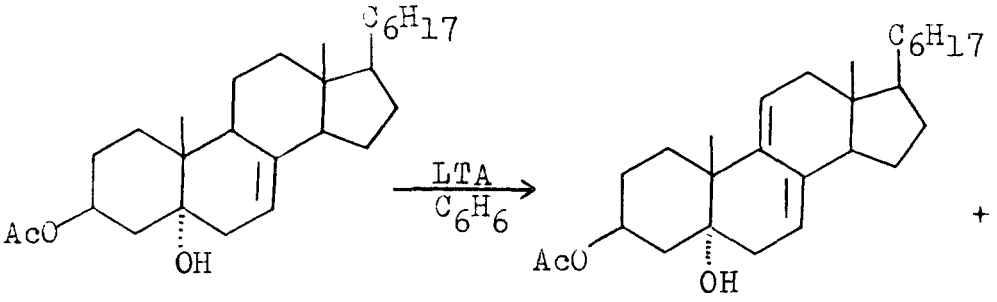


(XLVIII) (XLIX)

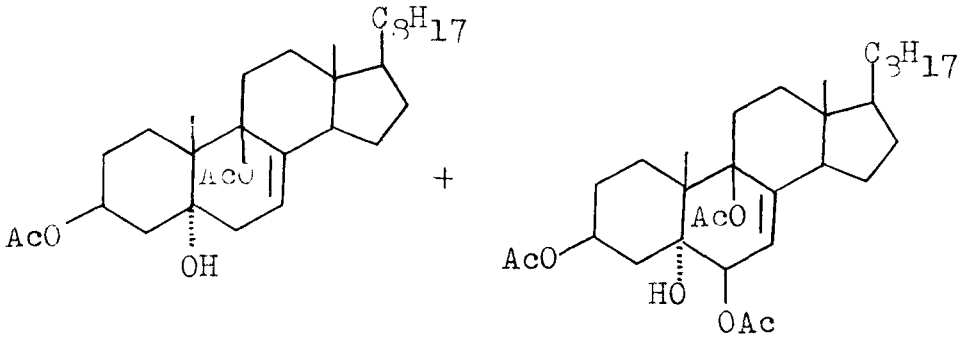
Photochemical oxidation of 3β,6α-diacetoxy-5α-cholest-7-en-5-ol (L) in benzene containing lead tetraacetate gave the secocholestenone (LI). Under similar reaction conditions, 3β-acetoxy-5α-cholest-7-en-5-ol (LII) gave (LIII-LV) via allylic oxidation and dehydrogenation[23].



(L) (LI)

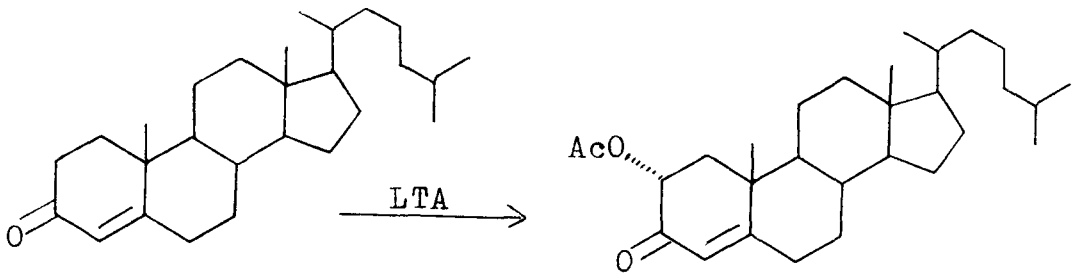


(LII) (LIII)

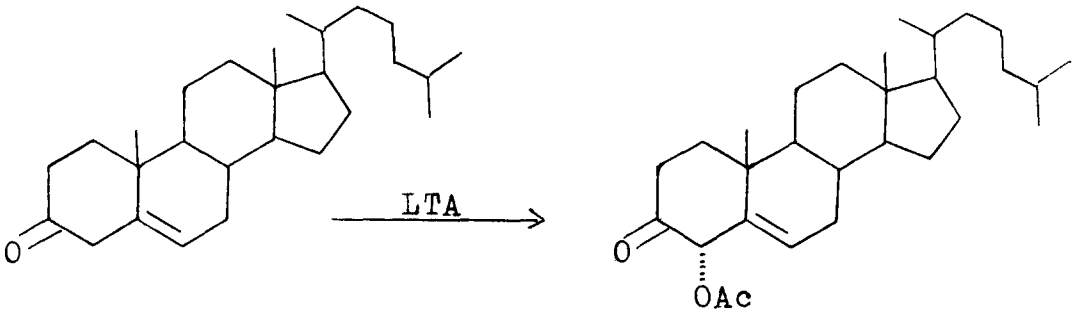


(LIV) (LV)

Introduction of acetoxy group at position α to a carbonyl group is illustrated by the following examples. Δ^4-Cholestene-3-one (LVIa) on treatment with lead tetraacetate, afforded a small amount of 2α-acetoxy-Δ^4-cholestene-3-one (LVII)[24]. Δ^5-Cholestene-3-one (LVIb) with lead tetraacetate at 15-25° gave Δ^5-cholestene-4α-ol-3-one acetate (LVIII) as the major product[25].

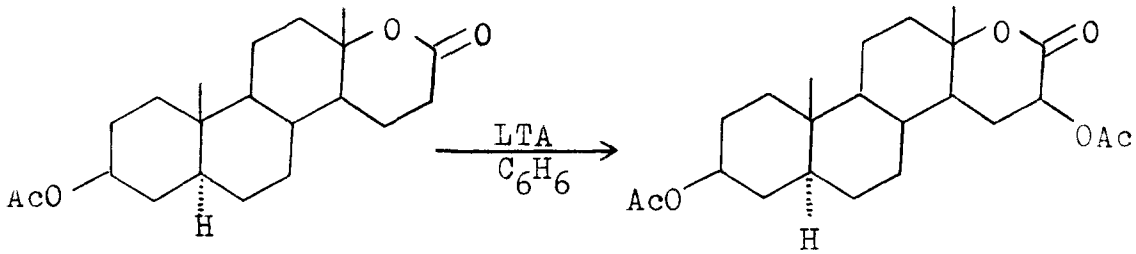


(LVIa) (LVII)



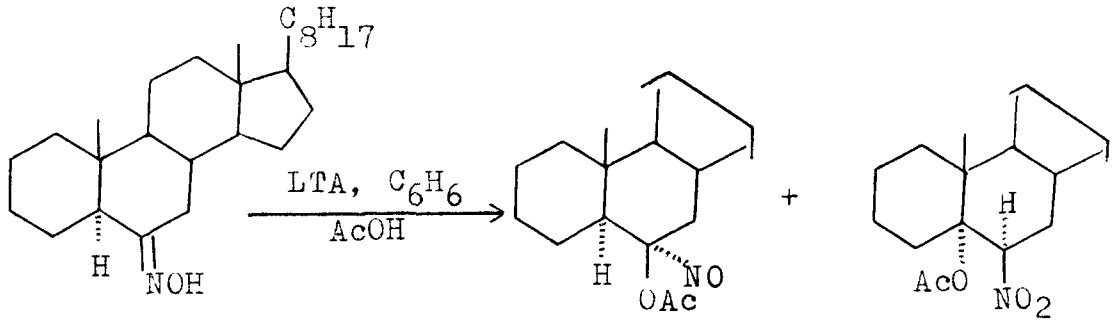
(LVIb) (LVIII)

α-Position to ketonic function of lactone ring was acetylated by lead tetraacetate. Thus 3β-acetoxy-13,17-seco-5α-androstan-13ξ-hydroxy-17-oic acid lactone (LIX) when treated with lead tetraacetate in benzene provided 3β,16β-diacetoxy-13,17-seco-5-androstan-13ξ-hydroxy-17-oic acid lactone (LX)[26].



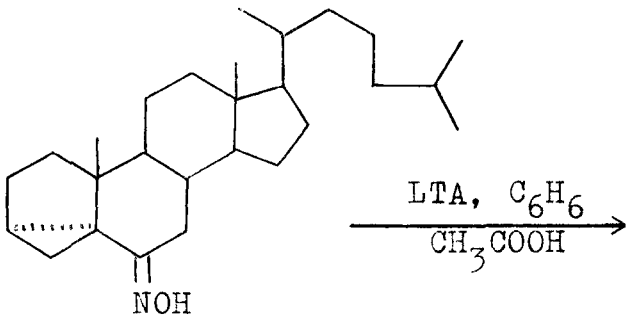
(LIX) (LX)

Reactions of lead tetraacetate with steroidal oximes were reported recently. 6-Oximino-5α-cholestane (LXI) when treated with lead tetraacetate in benzene and acetic acid provided 6β-acetoxy-6α-nitroso-5α-cholestane (LXII) and 5α-acetoxy-6β-nitrocholestane (LXIII)[27].

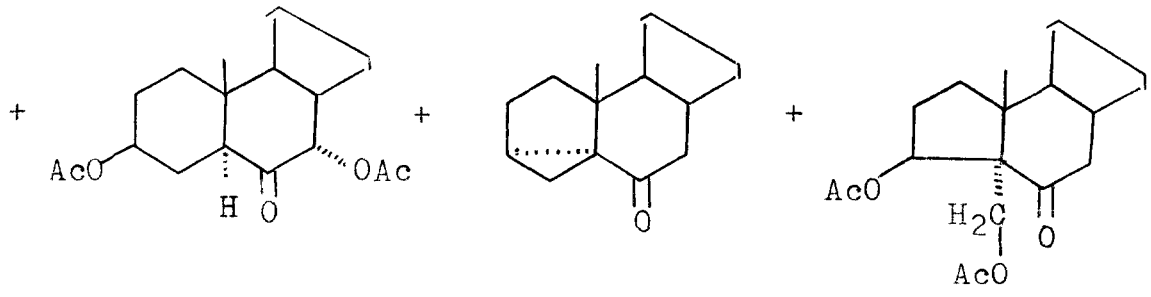


(LXI) (LXII) (LXIII)

When 3α,5-cyclo-6-oximino-5α-cholestane (LXIV) was subjected to similar treatment, yielded 3β,5-diacetoxy-5α-cholestan-6-one (LXV), 3β,7α-diacetoxy-5α-cholestan-6-one (LXVI), the parent ketone, 3α,5-cyclo-5α-cholestan-6-one (LXVII) and 3β-acetoxy-5-methyleneacetoxy-A-nor-5α-cholestan-6-one (LXVIII)[27].

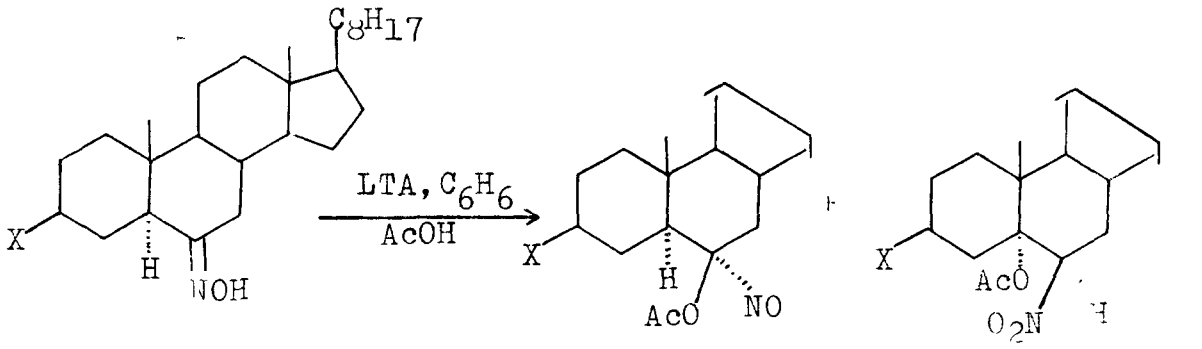


(LXIV) (LXV)



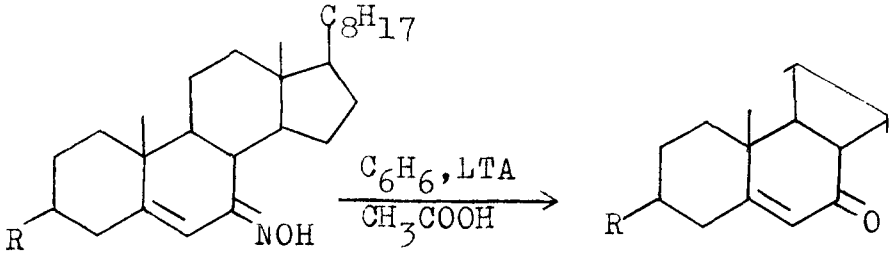
(LXVI) (LXVII) (LXVIII)

A number of steroidal oximes (LXIXa-d) when reacted with lead tetraacetate in benzene and acetic acid provided the corresponding 6β-acetoxy-6α-nitroso compounds (LXXa-d) along with 5-acetoxy-6β-nitro compounds (LXXIa-d)[28].



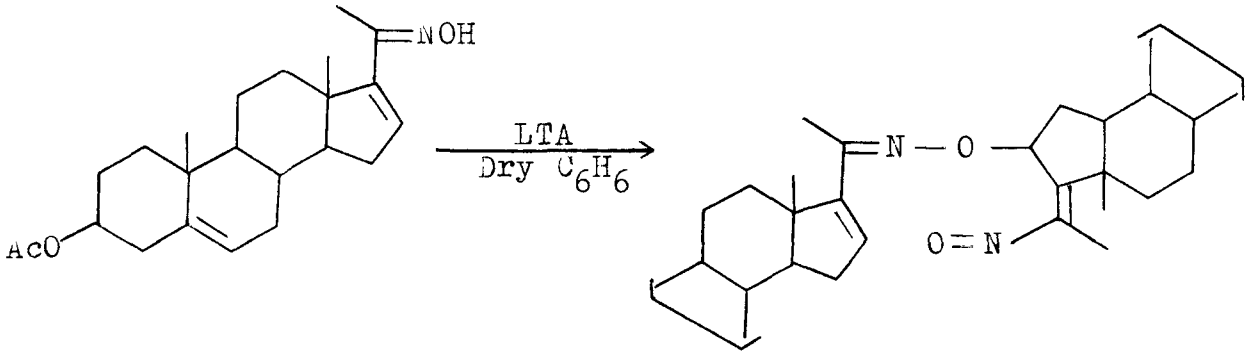
	X		X		X
(LXIXa)	-OAc	(LXXa)	-OAc	(LXXIa)	-OAc
(LXIXb)	-Cl	(LXXb)	-Cl	(LXXIb)	-Cl
(LXIXc)	-Br	(LXXc)	-Br	(LXXIc)	-Br
(LXIXd)	-I	(LXXd)	-I	(LXXId	-I

The reaction of α,β-unsaturated ketoximes (LXXII) and (LXXIII) with lead tetraacetate in benzene and acetic acid afforded exclusively the corresponding ketones (LXXIV) and (LXXV)[29] (deoximation product).

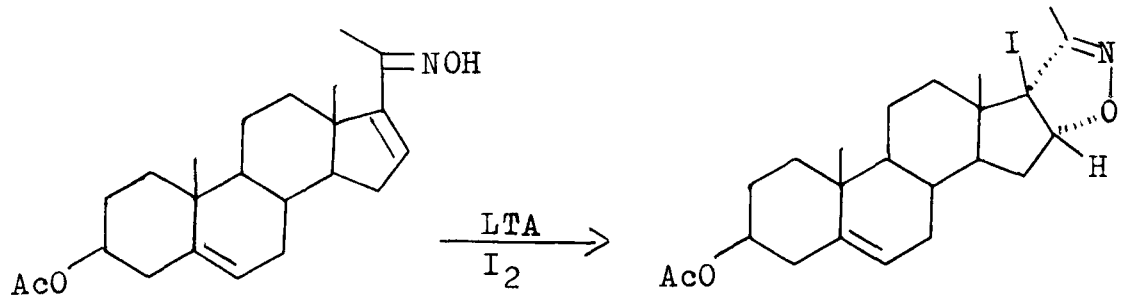


R		R	
(LXXII)	-OAc	(LXXIV)	-OAc
(LXXIII)	-Cl	(LXXV)	-Cl

Kaufmann et al.[30] showed that oxidation of 3β-acetoxy-pregna-5,16-dien-20-one oxime (LXXVI) with lead tetraacetate in dry benzene provided a dimeric compound (LXXVII) which was biologically active. Oxidation of (LXXVI) with lead tetra-acetate in the presence of iodine and small amount of water afforded an iodinated isoxazoline derivative (LXXVIII) as the product.

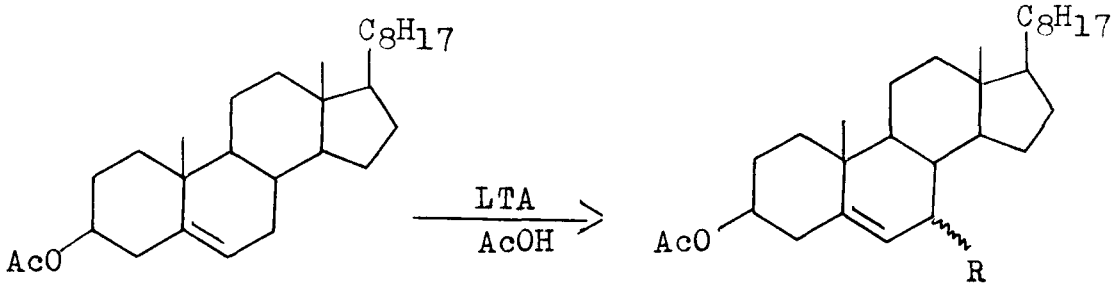


(LXXVI) (LXXVII)



(LXXVI) (LXXVIII)

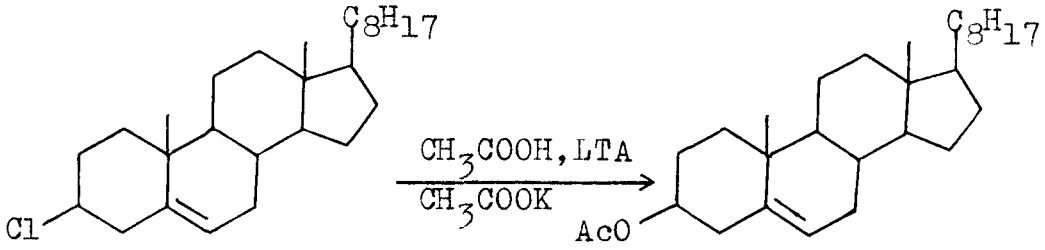
Mihailovic et al.[31] treated 3β-acetoxycholest-5-ene (LXXIX) with lead tetraacetate in glacial acetic acid and isolated 3β,7β-diacetoxycholest-5-ene (LXXX) and 3β,7α-diacetoxycholest-5-ene (LXXXI).



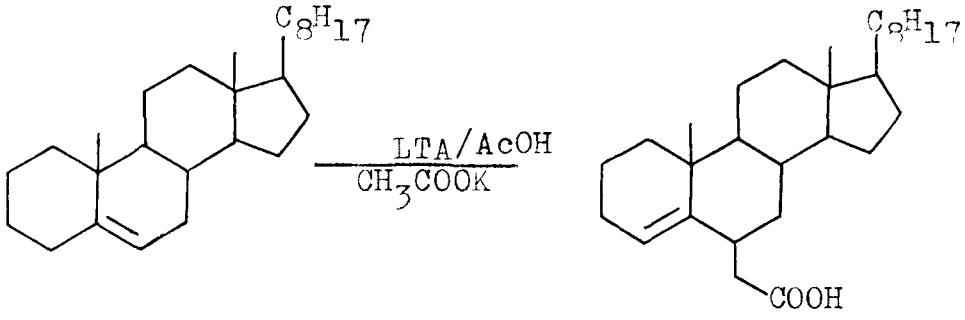
(LXXIX)

	R
(LXXX)	7β-acetoxy
(LXXXI)	7α-acetoxy

3β-Chlorocholest-5-ene (LXXXII) and cholest-5-ene (LXXXIV) when treated with lead tetraacetate in the presence of potassium acetate afforded 3β-acetoxycholest-5-ene (LXXXIII) and 6β-carboxymethylcholest-4-ene (LXXXV) respectively[32].

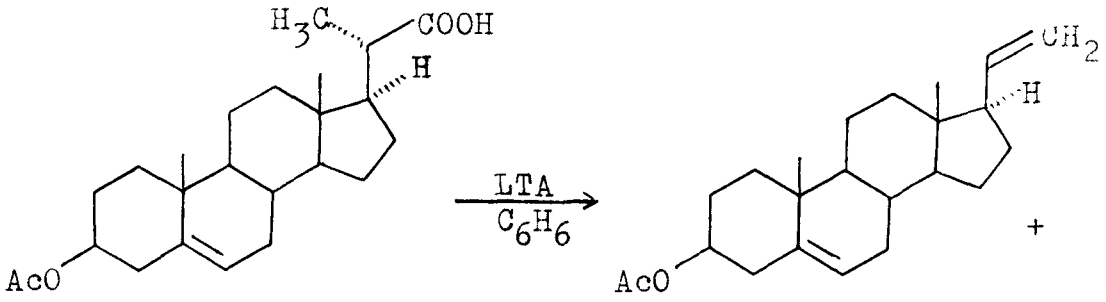


(LXXXII) (LXXXIII)

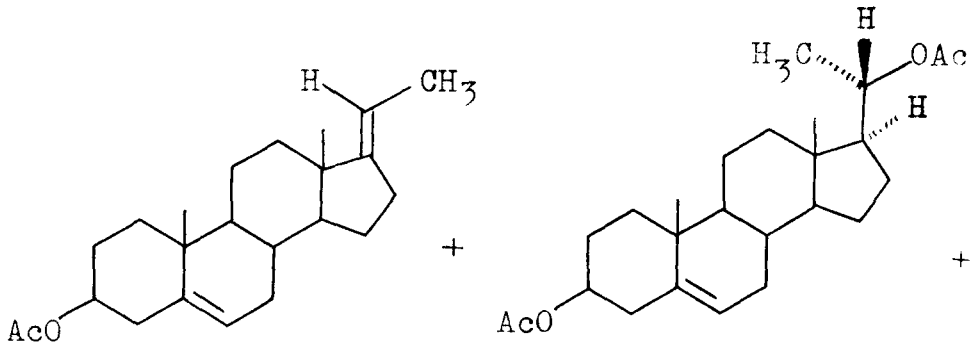


(LXXXIV) (LXXXV)

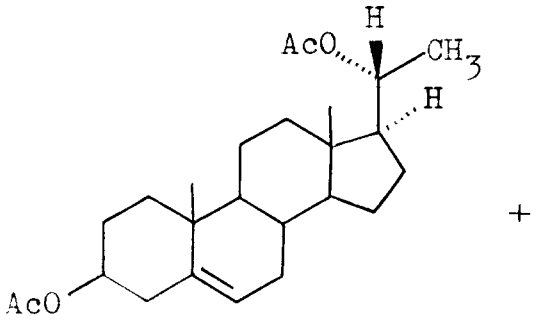
Sato Yashihiro and his coworker[33] have reported that the reaction of 3β-acetoxybisnorchol-5-enic acid (LXXXVI) with lead tetraacetate in benzene gave the isomeric pregnadienes (LXXXVII and LXXXVIII) and isomeric acetoxy derivatives (LXXXIX and XC). A trace of 3β-acetoxypregn-5-en-20-one and a dimer (XCI) also have been reported to be formed.



(LXXXVI) (LXXXVII)

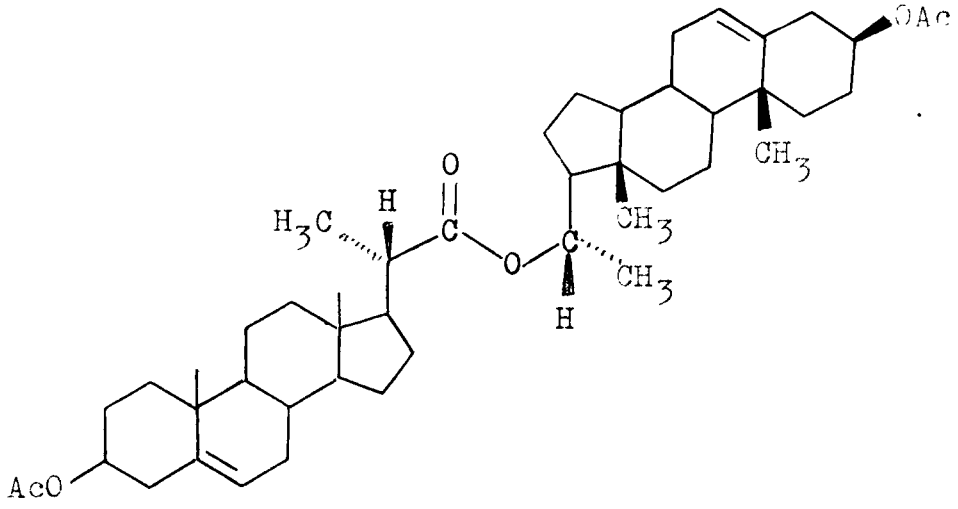


(LXXXVIII) (LXXXIX)



+

(XC)

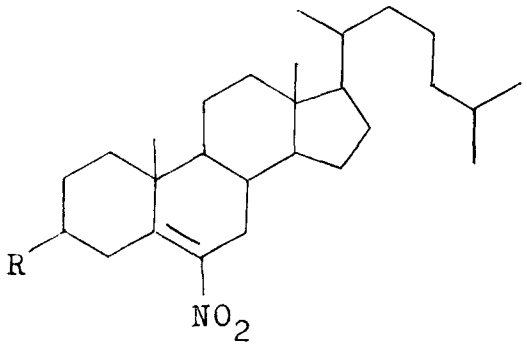


(XCI)

Discussion

A large number of papers describing the reactions of lead tetraacetate with steroidal alcohols[13-23], ketones[24,25] and oximes[27-30] have appeared at different intervals. No mention has been made about the reaction with nitro compounds. Mihailović et al.[31] observed that the double bond of steroid was not affected by the action of lead tetraacetate. But Heiba et al.[34] studied the action of lead tetraacetate on a simple olefin in which the double bond was greatly affected. Keeping these observations in view we carried out the reactions of lead tetraacetate with steroidal nitroolefins, to find out the effect of nitro group on the course of the reaction.

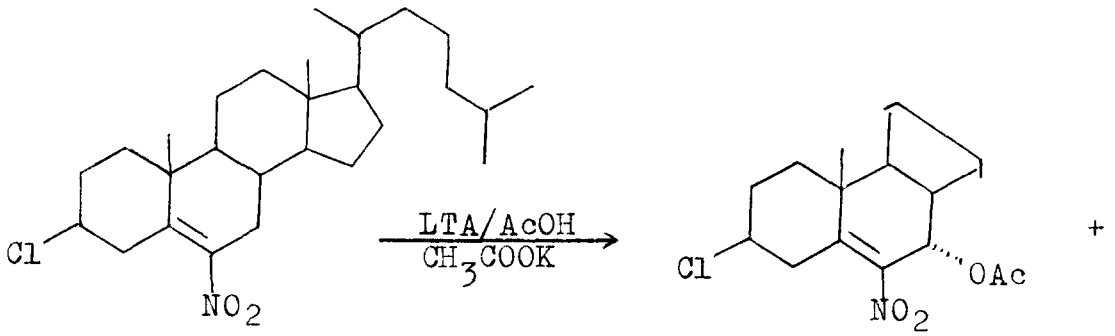
The present work deals with the reaction of lead tetraacetate with the easily accessible steroidal nitroolefins viz., 3β-chloro-6-nitrocholest-5-ene (XCII), 3β-acetoxy-6-nitrocholest-5-ene (XCIII) and 6-nitrocholest-5-ene (XCIV).



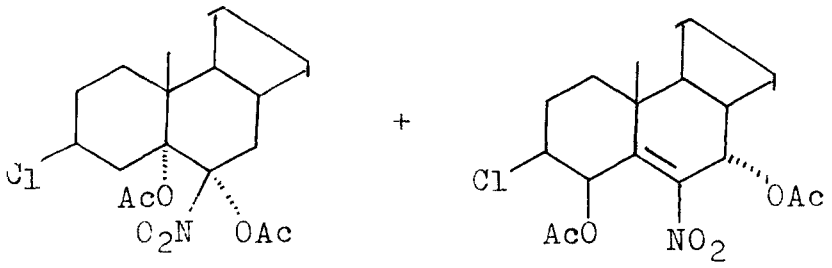
	R
(XCII)	Cl
(XCIII)	OAc
(XCIV)	H

Reaction of 3β-chloro-6-nitrocholest-5-ene (XCII) with lead tetraacetate-potassium acetate

3β-Chloro-6-nitrocholest-5-ene (XCII) was treated with lead tetraacetate in the presence of potassium acetate under reflux for 12 hours,(conditions reported by Heiba et al.[34]). The reaction mixture after work up and column chromatography over silica gel provided three compounds as non crystallizable oils (XCV, XCVI and XCVII).



(XCII) (XCV)



(XCVI) (XCVII)

Characterization of compound (XCV) as 3β-chloro-7α-acetoxy-6-nitrocholest-5-ene

The oily compound XCV was analysed for $C_{29}H_{46}NO_4Cl$ (positive Beilstein test). Its IR spectrum revealed the absorption bands at 1745, 1270-1210 cm^{-1}[35] indicating the attachment of acetoxy group to the molecule. The bands at 1630 (C=C), 1510 and 1365 cm^{-1} (C-NO_2)[37] showed that the nitro group was intact and the olefinic function was unaltered. The band at 710 cm^{-1} was for C-Cl stretchings. NMR spectrum was more helpful in arriving at the position of the acetoxy group. A broad singlet at δ 5.65 integrating for one proton was assigned to C7-proton. The drieding model of XCV showed the dihedral angle between C7-β$\underline{H}$ and C8-β$\underline{H}$ to be almost 90° which accounts for the non split signal of the C7-β$\underline{H}$[36]. Therefore the acetoxy group at C7 is axial, (α) oriented. A multiplet for one proton at δ 3.50 was assigned to C3-α$\underline{H}$ ($W_{\frac{1}{2}}$ = 18Hz; axial). A sharp singlet at δ 2.1 integrating for three protons was assigned to the acetoxy group. Methyl signals were seen at δ 1.15(C10-C$\underline{H}_3$), 0.68 (C13-C$\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons). On the basis of the foregoing discussion the compound (XCV) may be regarded as 3β-chloro-7α-acetoxy-6-nitrocholest-5-ene.

Characterization of the oil (XCVI) as 3β-chloro-5,6α-diacetoxy-6-nitro-5α-cholestane

The oily compound XCVI was analysed for $C_{31}H_{50}NO_6Cl$.

Positive Beilstein test showed the presence of chlorine. Its IR spectrum exhibited strong bands at 1730, 1280-1220 cm^{-1}. These data showed the addition of two acetoxy groups to the molecule. There were bands at 1510, 1365 ($C-NO_2$)[37] and 715 cm^{-1} (C-Cl) and there was no band in the region for carbon-carbon unsaturation which confirmed the attachment of two acetoxy groups to the olefinic system (at C5 and C6) and also the retainment of the nitro group. This was further supported by its NMR spectrum, which gave a multiplet at δ 4.10 integrating for one proton which was assigned to C3-α$\underline{H}$ (axial; $W_{\frac{1}{2}}$ = 18Hz). A strong singlet at δ 1.96 (with two notches at 2.0 and 1.93) integrating for six protons was assigned to the two acetoxy groups at C5 and C6. The configuration of the C5 acetoxy group has been considered as axial on the basis of the C3 proton which is axial (α) oriented and the trans A/B ring junction[36] rendered the C5 acetoxy group α-orineted. Other signals were at δ 1.16 (C10-C$\underline{H}_3$), 0.68 (C13-C$\underline{H}_3$), 0.93 and 0.81 (remaining methyl protons). On the basis of these spectral evidences the structure of the compound XCVI may be confirmed as 3β-chloro-5,6α-diacetoxy-6-nitro-5-cholestane.

Characterization of the compound XCVII as 3β-chloro-4β,7α-diacetoxy-6-nitrocholest-5-ene

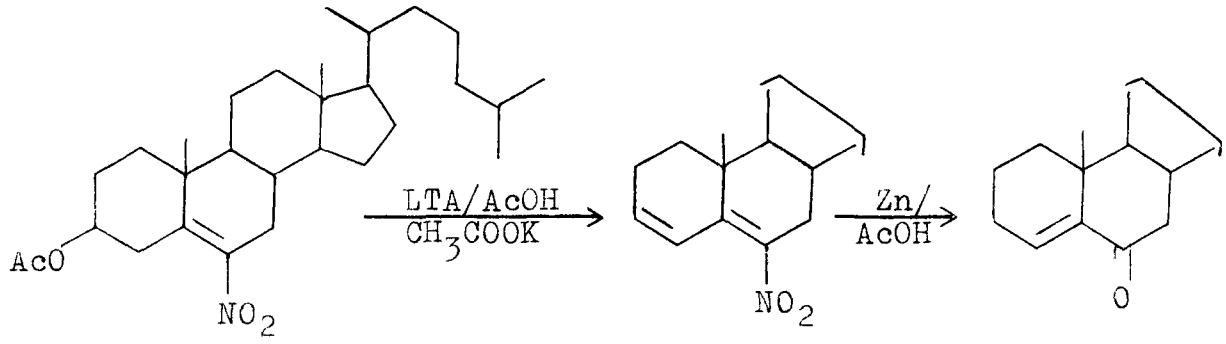
The oily compound XCVII was analysed for $C_{31}H_{48}NO_6Cl$ (positive Beilstein test). The insertion of two acetoxy groups was indicated by its elemental analysis and also by its IR

spectrum in which strong bands at 1730, 1280-1220 cm^{-1} were exhibited.for two acetoxy groups. The nitro group attached to the olefinic function remained unaltered as indicated by bands at 1645 (C=C), 1510 and 1370 cm^{-1} ($C-NO_2$). The band at 740 cm^{-1} was for C-Cl. In its NMR spectrum, a broad singlet at δ 4.50 was assigned to C7-β<u>H</u>. The half band width of 3Hz revealed that C7-β<u>H</u> is equatorial rendering axial (α) orientation to the acetoxy group at C7. A broad singlet ascribable to C3-α<u>H</u> appeared at δ 4.26 ($W_{\frac{1}{2}}$ = 8Hz; axial). A doublet at δ 5.76 (J = 3Hz) appeared which was assigned to C4-α<u>H</u> (equatorial). A singlet at δ 2.03 with two notches at δ 1.96 and 2.10 appeared corresponds to two acetoxy groups at C4 and C7. Other signals were seen at δ 1.26 (C10-C<u>H</u>$_3$), 0.70 (C13-C<u>H</u>$_3$), 0.95 and 0.85 (remaining methyl protons). The above data supports that the compound XCVII to be 3β-chloro-4β,7α-diacetoxy-6-nitrocholest-5-ene.

It is commendable that in the reaction of lead tetra-acetate with the above discussed steroidal nitro olefin (XCII) apart from the allylic substituted products formed (XCV and XCVII) (which is a usual course in these types of reactions), addition product (XCVI) was also formed which is in agreement with the observations previously made[34], where the olefinic system was greatly affected.

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XCIII) with lead tetraacetate-potassium acetate

3β-Acetoxy-6-nitrocholest-5-ene (XCIII) was treated with lead tetraacetate in acetic acid in the presence of potassium acetate. The reaction mixture was worked up and column chromatographed over silica gel to provide compound (XCVIII) m.p.72°.



(XCIII) (XCVIII) (XCIX)

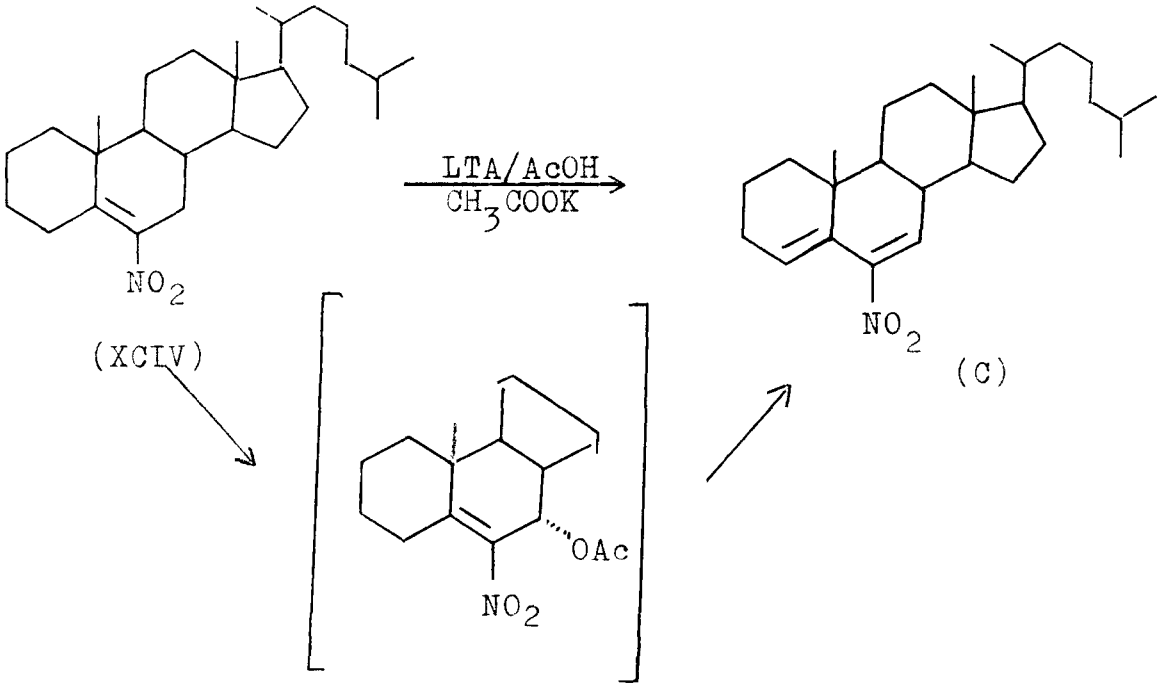
Characterization of the compound m.p. 72° as 6-nitrocholesta-3,5-diene (XCVIII)

Elemental analysis of the compound m.p. 72° corresponded to the molecular formula $C_{27}H_{43}NO_2$. Bands at 1680 (C=C-C=C)[37], 1508 and 1360 cm^{-1} (C=C-NO_2) in its IR spectrum indicated the creation of a double bond in conjugation to the previous one, by the elimination of the acetoxy group (as acetic acid). Its NMR spectrum exhibited a doublet at δ 6.5 which was assigned

to C4-H (J = 10Hz) and a multiplet centred at 6.3 (C3-H). The methyl signals were observed at δ 1.0 (C10-CH_3), 0.70 (C13-CH_3, 0.95 and 0.83 (other methyl protons). On the basis of the above data and by comparison with the authentic sample[38] the compound m.p. 72° was characterized as 6-nitrocholesta-3,5-diene (XCVIII). The structure (XCVIII) was further supported by its conversion to the known ketone (XCIX)[39].

Reaction of 6-nitrocholest-5-ene (XCIV) with lead tetraacetate-potassium acetate

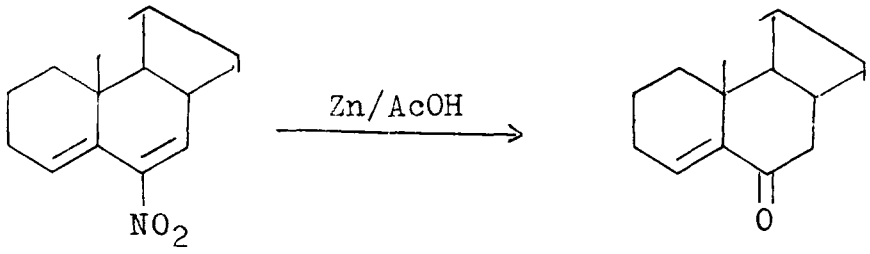
6-Nitrocholest-5-ene (XCIV) was refluxed with lead tetra-acetate in acetic acid in the presence of potassium acetate for 12 hours. After usual work up and column chromatography over silica gel a solid m.p. 76° was obtained in addition to some unreacted strating compound (XCIV).



(CI)

Characterization of the compound m.p. 76° as 6-nitrocholesta-4, 6-diene (C)

The compound m.p. 76° was analysed for $C_{27}H_{43}NO_2$. Its IR spectrum gave band at 1680 cm^{-1} which clearly indicated the creation of an additional double bond to give rise to a conjugated system. The bands at 1515 and 1365 cm^{-1} showed that the nitro group is intact. The NMR spectrum gave a multiplet at δ 5.75 ascribable for C4-H and a broad singlet at δ 5.30 for C7-H. Angular methyl protons were seen at δ 1.21 (C10-CH_3). 0.73 (C13-CH_3), 1.0 and 0.86 (remaining methyl protons). On the basis of the above evidences the compound m.p. 76° was characterized as 6-nitrocholesta-4,6-diene (C). The proposal was further supported by its conversion to the known ketone (XCIX)[39].



(C) (XCIX)

It is pertinent to mention here that in the case of 6-nitrocholest-5-ene also the reaction should have proceeded through a normal course to give rise to the α-substituted product (CI) which by subsequent elimination of acetic acid provided the diene (C).

Experimental

3B-Chloro-6-nitrocholest-5-ene

To a well stirred mixture of 3β-chlorocholest-5-ene (12 g), glacia acetic acid (80 ml) and nitric acid (25 ml; d, 1.52) at temperature below 20°, was added sodium nitrite (3.0 g) gradually over a period of 3 hours. After the complete addition of sodium nitrite, the mixture was further stirred for about 1 hour. Ice-cooled water (200 ml) was added and the yellowish solid thus separated was filtered and air dired. The desired product was recrystallized from methanol as needles (8.3 g), m.p. 151-152°C (reported[40] m.p. 153°).

Reaction of 3β-chloro-6-nitrocholest-5-ene (XCII) with lead tetra-acetate-potassium acetate: 3β-Chloro-7α-acetoxy-6-nitrocholest-5-ene (XCV), 3β-chloro-5,6α-diacetoxy-6-nitro-5α-cholestane (XCVI) and 3β-chloro-4β,7α-diacetoxy-6-nitrocholest-5-ene (XCVII)

A mixture of 3β-chloro-6-nitrocholest-5-ene (XCII) (2 g), lead tetraacetate (4 g) and anhydrous potassium acetate (1 g) in glacial acetic acid (150 ml) was refluxed for 12 hours. The reaction mixture was cooled to room temperature, diluted with ice-cooled water and extracted with ether. The ethereal solution was washed with sodium hydrogen carbonate solution (10/) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue which was chromatographed over silica gel (40 g). Elution with light petroleum ether:ether (20:1) furnished (XCV) as a non-crystable oil (600 mg).

Analysis Found : C, 78.35; H, 10.30; N, 3.38

$C_{29}H_{46}NO_4Cl$ requires : C, 78.45; H, 10.41; N, 3.28%

IR : $\nu_{max.}$ 1745, 1270-1210 (CH_3COO), 1630 (C=C), 1510, 1365 ($C-NO_2$) and 710 cm^{-1} (C-Cl)

NMR : δ 5.65 br,s(C7-β$\underline{H}$), 3.50 mc(C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 18Hz), 2.1 s ($C\underline{H}_3COO$), 1.15 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Further elution with light petroleum ether:ether (18:1) gave (XCVI) as an oil which failed to crystallize (700 mg).

Analysis Found : C, 65.40; H, 8.70; N. 2.43

$C_{31}H_{50}NO_6Cl$ requires : C, 65.49; H, 8.79; N, 2.46%

IR : $\nu_{max.}$ 1730, 1280-1220 (CH_3COO), 1510, 1365 ($C-NO_2$) and 715 cm^{-1} (C-Cl)

NMR : δ 4.10 (C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 18Hz), 1.96 (2 x $C\underline{H}_3COO$), 1.16 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.93 and 0.81 (remaining methyl protons).

Continued elution with light petroleum ether:ether (16:1) gave (XCVII) again as an oil which failed to crystallize(500 mg)

Analysis Found : C, 65.50; H, 8.43; N, 2.43

$C_{31}H_{48}NO_6Cl$ requires : C, 65.54; H, 8.45; N, 2.46%

IR : $\nu_{max.}$ 1730, 1280-1220 (CH_3-COO), 1645 (C=C), 1510, 1370 ($C-NO_2$) and 740 cm^{-1} (C-Cl)

NMR : δ 5.76 d(C4-α$\underline{H}$; J = 3Hz; equatorial), 4.50 br,s(C7-β$\underline{H}$; $W_{\frac{1}{2}}$ = 3Hz, equatorial), 4.26 br,s(C3-α$\underline{H}$; $W_{\frac{1}{2}}$ = 8Hz, axial)

2.03 (2 x $C\underline{H}_3COO$), 1.26 ($ClO\text{-}C\underline{H}_3$), 0.70 ($Cl3\text{-}C\underline{H}_3$), 0.95 and 0.85 (remaining methyl protons)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XCIII) with lead tetraacetate-potassium acetate: 6-Nitrocholesta-3,5-diene (XCVIII)

3β-Acetoxy-6-nitrochoest-5-ene (XCIII) (2 g), lead tetraacetate (4 g) and anhydrous potassium acetate (1 g) were refluxed in glacial acetic acid (150 ml) for 12 hours. The reaction mixture was worked up in the usual manner. Evaporation of the solvent gave a residue, which was chromatographed over a column of silica gel (40 g). Elution with light petroleum ether provided a solid (XCVIII) which was crystallized from light petroleum ether (1.2 g) m.p. 72°C (reported m.p.[38] 72-73°).

Analysis Found : C, 78.41; H, 10.45; N, 3.36

$C_{27}H_{43}NO_2$ requires : C, 78.45; H, 10.41; N, 3.38%

IR : $\nu_{max.}$ 1680 (C=C-C=C), 1508 and 1360 cm^{-1} ($C\text{-}NO_2$)

NMR : δ 6.5 d ($C4\text{-}\underline{H}$; J = 10Hz), 6.3 mc ($C3\text{-}\underline{H}$), 1.0($ClO\text{-}C\underline{H}_3$), 0.70($Cl3\text{-}C\underline{H}_3$), 0.95 and 0.83 (remaining methyl protons).

Reaction of 6-nitrocholesta-3,5-diene (XCVIII) with Zn/AcOH: Cholest-4-en -6-one (XCIX)

To a solution of 6-nitrocholesta-3,5-diene (XCVIII)(1.0 g) in hot glacial acetic acid (20 ml), zinc dust (2 g) was added gradually in small portions with shaking. The suspension was heated under reflux for 2 hours and water (2 ml) was added at

regular intervals during the course of heating. The hot solution was filtered and the filtrate was cooled to room temperature. It was diluted with large excess of ice-cooled water and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (10%) and water and dried (anhydrous sodium sulphate). Evaporation of the solvent furnished an oil which on crystallization from ethanol furnished cholest-4-en-6-one (XCIX) (700 mg), m.p. 108° (reported[39] m.p. 106-108°).

Cholest-5-ene

3β-Chlorocholest-5-ene (15.0 g) was dissolved in warm amyl alcohol (300 ml) and sodium metal (35.0 g) was added in small portions to the solution with continuous stirring over a period of 8 hours. The reaction mixture was heated occasionally during the course of the reaction in order to keep the sodium metal dissolved. The reaction mixture was poured into water, acidified with HCl and allowed to stand overnight. A white crystalline solid was obtained, which was filtered under suction and washed thoroughly with water and air dried. Recrystallization of the crude product from acetone gave cholest-5-ene in cubes (10.8 g) m.p. 94-95°C (reported[41] m.p. 89.5-91.2°).

6-Nitrocholest-5-ene

A suspension of finely powdered cholest-5-ene (3.0 g) in

glacial acetic acid (25 ml) was stirred at room temperature for 5 minutes. Fuming nitric acid (10 ml, d, 1.52) was added and the stirring was continued for 2 hours. The temperature of the reaction mixture was controlled between 20-25° by external cooling. The reaction mixture was then poured into ice-cooled water. An yellow solid thus obtained was filtered under suction, washed thoroughly with water and air dried. Recrystallization from ethanol furnished the desired compound (1.6 g), m.p. 117-118° (reported[42] m.p. 117-118°).

Reaction of 6-nitrocholest-5-ene (XCIV) with lead tetraacetate-potassium acetate:6-Nitrocholesta-4,6-diene (C)

6-Nitrocholest-5-ene (XCIV)(2.0g), lead tetraacetate(4.0 g) and anhydrous potassium acetate (1.0 g) were refluxed in glacial acetic acid (150 ml) for 12 hours. After usual work up an oily residue was obtained which was chromatographed on a column of silica gel (40.0 g). Elution with light petroleum ether gave a solid (C) which was recrystallised from light petroleum ether (1.1 g) m.p. 76°.

Analysis Found : C, 78.40; H, 10.36; N, 3.42

$C_{27}H_{43}NO_2$ requires : C, 78.45; H, 10.41; N, 3.38%

IR : $\nu_{max.}$ 1680 (C=C-C=C), 1515 and 1365 cm^{-1} (C-NO_2)

NMR : δ 5.75 mc(C4-H), 5.30 br,s(C7-H), 1.21(C10-CH_3), 0.73 (C13-CH_3), 1.0 and 0.86 (remaining methyl protons).

Reaction of 6-nitrocholesta-4,6-diene (C) with Zn/AcOH: Cholest-4-en-6-one (XCIX)

To a solution of 6-nitrocholesta-4,6-diene (C) (1.0 g) in hot glacial acetic acid (20 ml) was added zinc dust (2.0 g) in small portions and refluxed for 2 hours. Water (2 ml) was added at regular intervals during the course of heating. The reaction mixture was worked up in ether in the usual manner. Evaporation of the solvent and crystallization of the crude product from ethanol provided cholest-4-en-6-one (XCIX) (600 mg) m.p. 108° (reported[39] m.p. 106-108°).

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